



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 32

A. R. Katritzky

Advances in  
**Heterocyclic  
Chemistry**

Volume 32

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Advances in

# HETEROCYCLIC CHEMISTRY

*Edited by*

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## Preface

Volume 32 consists of five chapters. Of these, that by Kurzer on "1,2,4-Thiadiazoles" updates his own contribution on this subject which appeared in 1965 in Volume 5.

The other four contributions all deal with topics that have not previously been reviewed in the series. Sammes and the series editor have written on "Isopyrroles," the nonaromatic isomers of pyrroles. Two contributions deal with aspects of thiophene reactions: Barker has summarized "Dithienylmethane" chemistry and Klemm has provided a comprehensive account of "Condensed Thiophenes." Finally, Albert has contributed "Compounds Containing a Fused Pyrimidine Ring," a chapter that includes many ring systems of pharmaceutical interest.

The literature has been covered through *Chemical Abstracts* to 1980 or later.

A. R. KATRITZKY

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# Annellation of a Pyrimidine Ring to an Existing Ring

ADRIEN ALBERT

*Department of Chemistry, Australian National University,  
Canberra, Australia*

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## I. Introduction

Substances with a fused pyrimidine ring, such as purines, pteridines, and riboflavin, play a very important part in the biochemistry of the living cell. Many candidate drugs have been modeled on these compounds, particularly for cancer and virus research. In addition, several antibiotics incorporating this chemical structure have been isolated.

The present chapter attempts to summarize reactions that can annelate a pyrimidine ring onto an existing ring; it is subdivided according to the groups present in the host ring. How to select, from all these reactions, the ones that can introduce a desired group into the pyrimidine ring can be gleaned from Table I. Except for those described in Section II, all reactions require the presence of an amino group in the parent ring. The substituent that stands ortho to this group governs the allocation of the other sections of the chapter. The subdivision of the sections depends on the type of reagent used to react with such pairs of substituents. Yet another approach is offered in the literature, although only in three areas—quinazolines,<sup>1</sup> purines,<sup>2</sup> and pyridopyrimidines<sup>3</sup>—for which methods of synthesis can be traced backward once the end product has been chosen.

The quantity of information relevant to this chapter is surprisingly large (the better part of a book has been devoted to reactions described here in Section VI).<sup>4</sup> This wealth of widely scattered material has necessitated selection and compression, as well as the omission of all examples in which a nitrogen atom is shared by two rings.

Particular attention is given to electronic disposition in the host ring, because this is the principal factor facilitating or opposing a chosen reaction; thus, it forms the most useful basis for choosing between alternative methods. It is fundamentally important for this purpose to distinguish between  $\pi$ -deficient and  $\pi$ -excessive heterocyclic rings.<sup>5</sup> In  $\pi$ -deficient rings (e.g., pyridine), the presence of a double-bonded nitrogen atom attracts electrons from the  $\pi$ -layer of the nucleus. This polarization leaves the carbon atoms positively charged and hence indifferent to electrophiles. Amino groups attached to these carbon atoms are drained of electrons and hence are resistant to electrophilic attack. Single-bonded nitrogen atoms in a ring, on the other hand, make the ring  $\pi$ -excessive and hence favorable to electrophilic attack. Pyrrole (11a) is an outstanding example of a  $\pi$ -excessive nucleus (furan and thiophene are also  $\pi$ -excessive).

The larger the number of double-bonded nitrogen atoms in a nucleus, the more  $\pi$ -deficient it becomes. Considerations of valency dictate that only double-bonded nitrogen atoms can be built into a  $\pi$ -excessive ring, and each one of these decreases the  $\pi$ -excessive character. Thus, imidazole (18) is less  $\pi$ -excessive than pyrrole, and 1,2,3-triazole (20) is strongly  $\pi$ -deficient. The

<sup>1</sup> W. L. F. Armarego, "Quinazolines," Wiley (Interscience), New York, 1967.

<sup>2</sup> J. H. Lister, "Purines," Wiley (Interscience), New York, 1971.

<sup>3</sup> D. G. Wibberley, *Adv. Heterocycl. Chem.* **10**, 149 (1969).

<sup>4</sup> E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," Wiley (Interscience), New York, 1970.

<sup>5</sup> A. Albert, "Heterocyclic Chemistry," 2nd ed. Athlone, London, and Oxford Univ. Press, New York, 1968.

**TABLE I**  
 LOCATION IN THE TEXT OF METHODS FOR  
 FORMING PYRIMIDINE RINGS BEARING  
 REQUIRED SUBSTITUENTS<sup>a</sup>

Position on pyrimidine ring		
2	4	Section <sup>b</sup>
—	—	II,A-C; III; V*
—	H <sub>2</sub>	IV,A,1-3*; IV, B*
H <sub>2</sub>	H <sub>2</sub>	IV,A,7*
NH <sub>2</sub> <sup>c</sup>	—	II,B,C; V*
NH <sub>2</sub>	R <sup>d</sup>	II,C; V*
—	NH <sub>2</sub>	V; VI,A,1-3*
NH <sub>2</sub>	NH <sub>2</sub>	II,A-C; III; VI,A,5*
O	—	II,C; III; V*
O	R	II,C; IV,A*; VII,C
—	O	II,B,C; III; V; VI,B,3; VII,A, 1-5*; VIII; XI
O	O	II,C; III; V; VII,A,6*; VIII,XI
O	NH <sub>2</sub>	II,A; VI,A,6*; X
NH <sub>2</sub>	O	II, A-C; VII,A,5*; VIII
S	—	II,B,C; V; VI,B,1*
S <sup>e</sup>	R	II,C; IV,A*
—	S	VII,C*; XI
S	O	II,B,C; VII,A,6*; VIII
O	S	VII,C
S	NH <sub>2</sub>	II,A; VI,A,6*
S	S	III; VI,B,2*
<i>Rarer substituents</i>		
CHO	—	XI
CO <sub>2</sub> H	—	IV,A,6; V
—	CO <sub>2</sub> H	II,B; V
—	CONH <sub>2</sub>	V; X
OMe (OEt)	—	V; VIII,A,6; VIII,B,6
NHCN	—	V
—	CN	X
—	Br	III

<sup>a</sup> Alkyl and aryl substituents have been ignored because the given methods usually cover C- and N-substituted homologs.

<sup>b</sup> An asterisk signifies the most frequently used method.

<sup>c</sup> NHMe groups included with NH<sub>2</sub> groups in each entry.

<sup>d</sup> R implies that the pyrimidine ring is dihydrogenated.

<sup>e</sup> SMe groups included with S groups in each entry.

dominance of  $\pi$ -deficiency is greater the more closely the heteroatoms are situated; e.g., 1,2,3-triazole is more so than 1,2,4-triazole.

In the following discussion, yields are defined as low (up to 25%), moderate (25–50%), good (50–75%), and excellent (over 75%). Formulas 1–22 depict the parent nuclei most frequently mentioned in the text and are placed



(1)  
Quinazoline



(2)  
Pyrimidine



(3)  
Pyrido[2,3-*d*]pyrimidine



(4)  
Pyrido[3,4-*d*]pyrimidine



(5)  
Pyrido[4,3-*d*]pyrimidine



(6)  
Pyrido[3,2-*d*]pyrimidine



(7)  
Pyrimidino[4,5-*d*]pyrimidine



(8)  
Pyrimidino[5,4-*d*]pyrimidine



(9)  
Pyrazine



(10)  
Pteridine



(11a) Pyrrole (X = NH)  
(11b) Furan (X = O)  
(11c) Thiophene (X = S)



(12)  
Pyrrolo(or furo or thieno)[2,3-*d*]pyrimidine  
(X = NH, O, or S, respectively)



(13)  
Pyrrolo(or furo or thieno)[3,4-*d*]pyrimidine  
(X = NH, O, or S, respectively)



(14)  
Pyrrolo(or furo or thieno)[3,2-*d*]pyrimidine  
(X = NH, O, or S, respectively)



(15)  
Pyrazole



(16)  
Pyrazolo[3,4-*d*]pyrimidine

(17)  
Pyrazolo[4,3-*d*]pyrimidine(18)  
Imidazole(19)  
Purine(20)  
*v*-Triazole  
(1,2,3-triazole)(21)  
8-Azapurine(22)  
*v*-Triazolo[4,5-*d*]pyrimidine  
(identical with 21)(23)  
Pyrid-4-one(24)  
2-Oxo-4-thioxopyrimidine-5-carboxylic acid

conveniently here to save duplication. Attention is drawn to the following conventions. The cyclic amide structure is designated as “-one” at the end of a name, e.g., pyrid-4-one (23), and not 4-oxopyridine, 4-oxo-1,4-dihydropyridine, or 4-hydroxypyridine. Similarly, the cyclic thioamide function is given the suffix “-thione.” But when both functions occur in the same molecule, the thioamide is denoted by “thioxo-” in the body of the name. When a carboxylic acid group is also present, this is given the terminal position so that any cyclic amide or thioamide groups must appear in the body of the name (e.g., 24). “Indicated hydrogen” is not given unless ambiguity would arise.

## II. From Rings Lacking an Amino Group

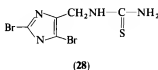
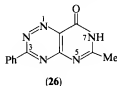
### A. FROM RINGS WITH A CHLORO, ALKOXY, OR METHYLTHIO SUBSTITUENT ADJACENT TO AN ESTER, ALDEHYDE, OR NITRILE GROUP

2-Chloro-3-methoxycarbonylpyrazine (see 9), when heated with guanidine carbonate without a solvent at 170°C for 30 min, gave an excellent yield of 2-aminopteridin-4-one (see 10), and the 5,6-diphenyl derivative of this

pyrazine behaved similarly. However, free guanidine in refluxing methanol gave only a poor yield.<sup>6</sup>

5-Chloro-6-ethoxycarbonyl-3-phenyl-1,2,4-triazine (**25**), heated with free acetamide at 120°C for 15 min, gave a moderate yield of 6-methyl-3-phenylpyrimidino[4,5-*e*]1,2,4-triazin-8-one (**26**). Benzamidine similarly gave the 6-phenyl analog in good yield, and NN'-dimethylurea similarly produced 5,7-dimethyl-3-phenylpyrimidino[4,5-*e*]1,2,4-triazine-6,8-dione (1 hr at 135°C).<sup>7</sup>

Instead of pairing the chloro substituent with an ester group, it can be used in conjunction with an aldehyde or nitrile group. Thus, 2-chloro-3-formylindole and formamide gave 9-*H*-pyrimidino[4,5-*b*]indole at 180°C.<sup>8</sup> Again, 2-chloro-3-cyano-5,6-diphenylpyrazine, fused with guanidine carbonate, gave a good yield of 2,4-diamino-6,7-diphenylpteridine (see **10**), whereas urea and thiourea fusions produced 4-amino-6,7-diphenylpteridin-2-one and 4-amino-6,7-diphenylpteridine-2-thione, respectively, in good yields.<sup>9</sup> Similarly, 5-chloro-6-cyano-3-phenyl-1,2,4-triazine (see **25**), refluxed



for 16 hr with free guanidine in methanol, gave a good yield of 2,4-diamino-7-phenylpyrimidino[4,5-*e*]1,2,4-triazine (also other examples in which the 3-substituent was varied).<sup>10</sup>

In another example, in which the chloro substituent is paired with a carbonyl group, 1-chloro-2-formylcyclohex-1-ene (**27**) and formamide at 180°C gave 5,6,7,8-tetrahydroquinazoline (see **1**).<sup>11</sup> An unusual pairing of a halogen with a thioureidomethyl group is the conversion of 2,4-dibromo-5-thioureidomethylimidazole (**28**) to 8-bromo-1,6-dihydro-2-methylthiopurine (see **19**) by boiling in ethanolic pyridine.<sup>12</sup>

<sup>6</sup> G. P. G. Dick and H. C. S. Wood, *J. Chem. Soc.*, 1379 (1955).

<sup>7</sup> M. Brugger, H. Wamhoff, and F. Korte, *Justus Liebigs Ann. Chem.* **758**, 173 (1972).

<sup>8</sup> K. E. Schulte, J. Reisch, and U. Stoess, *Arch. Pharm. (Weinheim, Ger.)* **305**, 523 (1972).

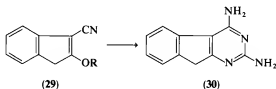
<sup>9</sup> E. C. Taylor and W. W. Paudler, *Chem. Ind. (London)*, 1061 (1955).

<sup>10</sup> E. C. Taylor and S. F. Martin, *J. Org. Chem.* **37**, 3958 (1972).

<sup>11</sup> W. Ziegenbein and W. Franke, *Angew. Chem.* **71**, 628 (1959).

<sup>12</sup> P. C. Mitter and N. Chatterjee, *J. Indian Chem. Soc.* **11**, 867 (1934).

Alkoxy as well as methylthio groups have sometimes been paired with a cyano group. Thus, 3-cyano-1-methyl-4-methylthiopyrid-2-one (see 23), refluxed for 12 hr with free guanidine in ethanol, furnished 2,4-diamino-6-methylpyrido[4,3-*d*]pyrimidin-5-one (see 5).<sup>13</sup> Again, 2-alkoxy-3-cyanoindenes (see 29), refluxed for 4 hr with free guanidine in ethanol, produced



denes (see 29), refluxed for 4 hr with free guanidine in ethanol, produced excellent yields of 2,4-diaminoindeno[2,1-*d*]pyrimidine with additional substituents in the benzene ring.<sup>14</sup>

#### B. FROM RINGS WITH AN ENDOCYCLIC KETO GROUP ADJACENT TO A REPLACEABLE HYDROGEN ATOM

This uncommon reaction requires a reagent with a positively charged carbon atom (e.g.,  $\text{N}\equiv\text{C}^+$ ) that is capable of electrophilic attack on the carbanion formed by loss of a proton from the alpha position of the ketone. Cyanoguanidine [ $\text{NCNHC}(\text{NH})\text{NH}_2$ ], known also as dicyandiamide, has this property as well as enough basic strength to extract the proton. When fused with cyclohexanone, cyanoguanidine gave 2,4-diaminoquinazoline (see 1).<sup>15</sup> Other cyclic ketones behaved similarly. *N,N*-Dialkyl derivatives of cyanoguanidine gave 4-amino-2-dialkylaminoquinazolines. Only reagents that retain one primary amino group can complete the pyrimidine ring through nucleophilic attack on the positively charged carbon atom of the carbonyl group. In all, the best times were from 3 to 6 hr, with temperatures (internal) varying from 155° to 205°C and giving moderate yields.<sup>15</sup>

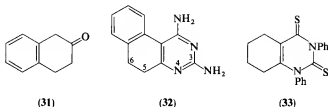
Similarly, eighteen 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines (e.g., 32) were made by fusion of 2-tetralones (e.g., 31) with cyanoguanidine. Average conditions were 190°–210°C (internal) for 30 mins. Yields ranged between low and good.<sup>16</sup>

<sup>13</sup> A. Kumar, H. Ila, and H. Junjappa, *J. C. S. Perkin I*, 857 (1978).

<sup>14</sup> A. Rosowsky, A. S. Day, J. Battaglia, and E. J. Modest, *J. Heterocycl. Chem.* **6**, 613 (1969).

<sup>15</sup> E. J. Modest, S. Chatterjee, and H. K. Protopapa, *J. Org. Chem.* **30**, 1837 (1965).

<sup>16</sup> A. Rosowsky, K. K. N. Chen, M. Papathanasopoulos, and E. J. Modest, *J. Heterocycl. Chem.* **9**, 263 (1972).



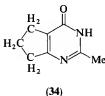
More difficult to explain is the production of 1,3-diphenyl-5,6,7,8-tetrahydroquinazoline-2,4-dithione (**33**) by heating cyclohexanone with *N,N'*-diphenylthiourea at 150°C (poor yield).<sup>17</sup>

**C. FROM RINGS WITH AN ENDOCYCLIC KETO GROUP ADJACENT  
TO AN EXOCYCLIC ESTER, KETONE, OR METHIDE (ALKYLIDENE)  
SUBSTITUENT OR FROM LACTONES OR LACTAMS**

**1. With Ester Side Chain**

Suitable reagents have two amino groups separated by a carbon atom. One amino group makes a nucleophilic attack on the electrophilic carbon atom of the keto group, whereas the other, by adding to the carbonyl group of the ester substituent, forms a tetrahedral complex that starts the exchange of  $\text{—NH}_2$  for  $\text{—OEt}$ .

5,6,7,8-Tetrahydroquinazolines are often made by this reaction (see **1** for numbering). Thus, 2-ethoxycarbonylcyclohexanone, refluxed with acetamidine in ethanolic sodium ethoxide, gave a good yield of 2-methyl-5,6,7,8-tetrahydroquinazolin-4-one.<sup>18</sup> 2-Ethoxycarbonylcyclopentanone similarly gave rise to the lower homolog, 2-methyl-5,6-trimethylenepyrimidin-4-one (**34**).<sup>18</sup> The same cyclohexanone, refluxed with guanidine in ethanolic sodium ethoxide, gave an excellent yield of 2-amino-5,6,7,8-tetrahydroquinazolin-4-one, and the same cyclopentanone similarly gave the lower homolog.<sup>19</sup>



<sup>17</sup> J. Schoen, *Rocz. Chem.* **29**, 549 (1955) [*CA* **50**, 8660 (1956)].

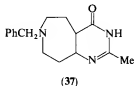
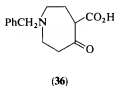
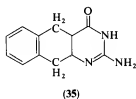
<sup>18</sup> G. E. McCasland and J. R. G. Bryce, *J. Am. Chem. Soc.* **74**, 842 (1952).

<sup>19</sup> R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman, and A. R. Todd, *J. Chem. Soc.*, 357 (1946).



2-Ethoxycarbonylcyclohexanone, refluxed with thiourea in ethanolic sodium methoxide (!), furnished 2-thioxo-5,6,7,8-tetrahydroquinazolin-4-one in good yield.<sup>20</sup> The same cyclohexanone and *S*-methylisothiuronium sulfate, in cold aqueous potassium hydroxide, gave a poor yield of 2-methylthio-5,6,7,8-tetrahydroquinazolin-4-one.<sup>21</sup>

Similarly, 3-carbomethoxy-2-tetralone, when refluxed with guanidine carbonate in ethanol for 16 hr, provided a moderate yield of 2-amino-5,10-



dihydrobenzo[*g*]quinazolin-4-one (35).<sup>22</sup> Heterocyclic ketones can also be used. For example, *N*-benzyl-5-ethoxycarbonyl-1-azacycloheptan-4-one (36), when refluxed with acetamidine in ethanolic sodium ethoxide, gave 7-benzyl-2-methyl-5,6,8,9-tetrahydropyrimidino[4,5-*d*]azepin-4-one (37) in good yield; guanidine and urea were used similarly.<sup>23</sup> Also, ethyl 1-methyl-4-oxopiperidine-3-carboxylate reacted with benzamidine, guanidine, and *S*-methylthiourea in aqueous potassium carbonate at 20°C to give 2*R*-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidines (where *R* = Ph, NH<sub>2</sub>, and SMe, respectively) in good yields.<sup>24</sup>

## 2. With Ketonic Side Chain

These intermediates have been used mainly to make quinazolines. Thus, 6-acetyl-3-methylcyclohex-2-enone (38), when boiled with guanidine carbonate in ethanol, gave 2-amino-4,7-dimethyl-5,6-dihydroquinazoline (yield not given).<sup>25</sup> 2-Oxocyclohexylglycolic acid (39), when boiled with guanidine

<sup>20</sup> B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.* **18**, 133 (1953).

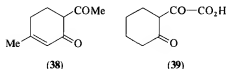
<sup>21</sup> F. H. S. Curd, D. N. Richardson, and F. L. Rose, *J. Chem. Soc.*, 378 (1946).

<sup>22</sup> A. Rosowsky, E. P. Burrows, P. C. Huang, and E. J. Modest, *J. Heterocycl. Chem.* **9**, 1239 (1972).

<sup>23</sup> H. Yamamoto, M. Nakata, S. Morosawa, and A. Yokoo, *Bull. Chem. Soc. Jpn.* **44**, 153 (1971).

<sup>24</sup> A. H. Cook and J. J. Reed, *J. Chem. Soc.*, 399 (1945); J. De Graw and L. Goodman, *Can. J. Chem.* **41**, 3137 (1963); K. Thomae, French Patents M 2798, 2928 (1964) [*CA* **62**, 6493, 9150 (1965)].

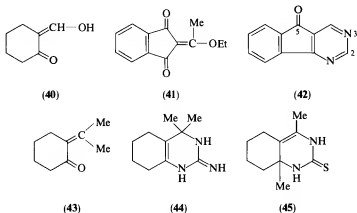
<sup>25</sup> R. N. Lacey, *J. Chem. Soc.*, 1625 (1960).



carbonate in aqueous methanol, produced 2-amino-5,6,7,8-tetrahydroquinazoline-4-carboxylic acid in good yield, and urea similarly furnished the 2-oxo analog.<sup>26</sup>

### 3. With Methide (Alkylidene) Side Chain

This reaction makes use of the addition of an amino group across a 1,3-enone system in the parent ring. A link with the previous section is furnished by 2-hydroxymethylenecyclohexanone (40), a tautomer of 2-formylcyclohexanone. When refluxed with guanidine carbonate in ethanol, it gave a



moderate yield of 2-amino-5,6,7,8-tetrahydroquinazoline.<sup>27</sup> Similarly, this ketone produced 5,6,7,8-tetrahydroquinazoline when heated with a mixture of formamide, trimethylmethane, and toluene-4-sulfonic acid (moderate yield).<sup>28</sup> 2-Ethoxymethylenecyclohexanone, stirred with guanidine in ethanolic sodium ethoxide at room temperature, gave a moderate yield of 2-amino-5,6,7,8-tetrahydroquinazoline, and the 6-methyl homolog was made similarly.<sup>29</sup>

<sup>26</sup> W. L. F. Armarego and B. A. Milloy, *J. C. S. Perkin I*, 2814 (1973).

<sup>27</sup> E. Benary, *Ber. Dtsch. Chem. Ges.* **63**, 2601 (1930).

<sup>28</sup> W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc. C*, 1635 (1969).

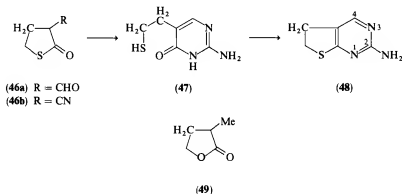
<sup>29</sup> K. Tsuda, S. Ikuma, M. Kawamura, R. Tachikawa, and T. Miyadera, *Chem. Pharm. Bull.* **10**, 868 (1962).

2-(1-Ethoxyethylidene)indandione (**41**) and formamidine, in methanolic sodium methoxide at room temperature, gave a good yield of 4-methylindeno[1,2-*d*]pyrimidin-5-one (**42**). Similarly, acetamidine, guanidine, and methylisothiourea furnished the 2-methyl, 2-amino, and 2-methylthio derivatives, respectively. Urea and thiourea failed to react.<sup>30</sup>

The  $\alpha,\beta$ -unsaturated ketonic structure of the parent is even clearer in the next two examples. 2-Isopropylidenecyclohexanone (**43**), when heated at 80°C with guanidine, gave an excellent yield of 2-imino-4,4-dimethyl-3,4,5,6,7,8-hexahydroquinazoline (**44**). With ammonium thiocyanate in boiling toluene and with urea at 40°C in a current of hydrogen chloride gas, good yields of the corresponding 2-thione and 2-one, respectively, were obtained. Similarly, 2-acetyl-1-methylcyclohexanone and ammonium thiocyanate provided a moderate yield of 4,8a-dimethyl-3,4,5,6,7,8,8a-hexahydroquinazoline-2-thione (**45**).<sup>31</sup>

#### 4. With Lactones and Lactams

A wealth of new ring systems becomes available when lactones (also thiolactones) and lactams are substituted for the benzenoid ketones. For example,  $\alpha$ -formyl- $\gamma$ -butyrolactone (**46a**), when refluxed with guanidine in ethanolic sodium ethoxide, underwent ring opening and recycling to give 2-amino-5-(2-mercaptoethyl)pyrimidin-6-one (**47**), which polyphosphoric acid converted (almost quantitatively at 95°C) to 2-amino-5,6-dihydrothiopheno[2,3-*d*]pyrimidine (**48**).<sup>32</sup> By substituting —CN for —CHO in the starting material (giving **46b**), the 4-amino derivative of **48** was produced,



<sup>30</sup> S. Demerac, L. K. Dalton, and B. C. Elmes, *Aust. J. Chem.*, **25**, 2651 (1972).

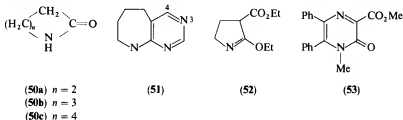
<sup>31</sup> W. Wendelin, A. Harler, and A. Fuchsgruber, *Monatsh. Chem.*, **107**, 141 (1976).

<sup>32</sup> H. Wamhoff and F. Korte, *Chem. Ber.*, **99**, 872 (1970).

whereas ketones corresponding to the aldehyde (46a) gave 4-alkyl analogs of 48. In the same project, guanidine was replaced, in turn, by acetamidine, urea, and thiourea, which replaced the 2-amino group by —Me, =O, and =S, respectively. When the related six-membered-ring thiolactones were substituted for 46, the products were 6,7-dihydrothiopyrano[2,3-*d*]pyrimidines.<sup>32</sup>

The same project also made use of the corresponding lactones (49), which opened to give hydroxy analogs of 47 when refluxed with guanidine in ethanolic sodium ethoxide. As before, polyphosphoric acid at 95°C effected cyclization, and the product was 2-amino-4-methyl-5,6-dihydro-furano[2,3-*d*]pyrimidine. The related six-membered-ring lactone produced the corresponding pyrano[2,3-*d*]pyrimidine. The yields in all this work were variable, mainly good to excellent.<sup>32</sup>

Lactams have given similar products but, being more stable than lactones, may function simply through activation of the methylene group by the neighboring carbonyl function. Thus, heating pyrrolid-2-one (50a) with formamide and phosphoryl chloride at 120°C, in a sealed vessel, produced 5,6-dihydropyrrolo[2,3-*d*]pyrimidine (see 12). The higher homologs, 50b



and 50c, gave 5,6,7,8-tetrahydropyrrolo[2,3-*d*]pyrimidine (see 3) and 5,6,7,8-tetrahydropyrimidino[4,5-*b*]azepine (51), respectively (undisclosed yields).<sup>33</sup>

The *O*-ethers of lactams have also been used. Thus, 2-ethoxy-3-ethoxycarbonyl-4,5-dihydropyrrole (52) was condensed with thiourea to give 2-thioxo-5,6-dihydropyrrolo[2,3-*d*]pyrimidin-4-one (see 12).<sup>34</sup> A higher homolog, 2-ethoxy-3-ethoxycarbonyl-3,4,5,6-tetrahydropyridine (a valerolactim ether) was condensed with guanidine to form 2-amino-5,6,7,8-tetrahydropyrrolo[2,3-*d*]pyrimidin-4-one (see 3).<sup>35</sup> The next higher homolog, 2-ethoxy-3-ethoxycarbonyl-3,4,5,6-tetrahydroazepine (a caprolactim ether) reacted with urea to give 5,6,7,8-tetrahydropyrimidino[4,5-*b*]azepine-2,4-dione (see 51); thiourea and guanidine reacted similarly, all in excellent

<sup>33</sup> K. Morita, S. Kobayashi, H. Shimadzu, and M. Ochai, *Tetrahedron Lett.*, 861 (1970).

<sup>34</sup> V. G. Granik and R. G. Glushkov, *Khim. Farm. Zh.* 1, 18, 21 (1967) [*CA* 68, 12941 (1968)].

<sup>35</sup> B. M. Pyatin and R. G. Glushkov, *Khim. Farm. Zh.* 2, 17 (1968) [*CA* 70, 28887 (1969)].

yields.<sup>34</sup> Again, 3-cyano-2-ethoxy-3,4,5,6-tetrahydroazepine and guanidine provided 2,4-diamino-5,6,7,8-tetrahydropyrimidino[4,5-*b*]azepine in moderate yield.<sup>34</sup>

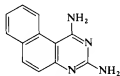
A more aromatic type of lactam, 3-methoxycarbonyl-1-methyl-5,6-diphenylpyrazin-2-one (53), when fused with guanidine carbonate, gave an excellent yield of 2-imino-8-methyl-6,7-diphenylpteridin-4-one (see 10).<sup>36</sup>

### III. From Rings with an Amino Group Adjacent to a Replaceable Hydrogen Atom

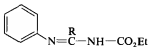
This section brings together a miscellaneous set of reactions all of which require a parent nucleus that is aromatic,  $\pi$ -excessive, and electronically equipped to support an electrophilic attack adjacent to the amino group. Understandably, rather severe conditions are often required. Common substituents found in the product are alkyl, aryl, amino, and oxo groups. For example, 2-aminonaphthalene hydrochloride, when refluxed for 2 days with an excess of sodium dicyanamide [ $\text{NaN}(\text{CN})_2$ ] in octanol, gave 1,3-diaminobenzo[*f*]quinazoline (54) in good yield; the method was also suitable for 1-aminonaphthalene and 1-aminoanthracene.<sup>37</sup>

Acetanilide, heated with urethane and phosphorus pentoxide, gave 2-methylquinazolin-4-one (see 1); benzanilide similarly furnished the 2-phenyl analog (yields not reported).<sup>38</sup> The intermediate is apparently the amidine 55, because this produced 2-phenylquinazolin-4-one, in moderate yield, when heated at 185°C.<sup>39</sup>

*N*-3-Methoxyphenyl-*N'*-acetylurea gave 5-methoxy-4-methylquinazolin-2-one (see 1) in polyphosphoric acid at 130°C (no yield given).<sup>40</sup>



(54)



(55)



(56)

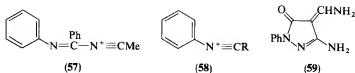
<sup>36</sup> G. P. G. Dick, W. E. Fidler, and H. C. S. Wood, *Chem. Ind. (London)*, 1424 (1956).

<sup>37</sup> A. Rosowsky and M. Papathanasopoulos, *J. Org. Chem.* **39**, 3293 (1974).

<sup>38</sup> M. Sen and J. Ray, *J. Chem. Soc.*, 646 (1926); T. Bhattacharaya, P. K. Bose, and J. N. Ray, *J. Indian Chem. Soc.* **6**, 279 (1929).

<sup>39</sup> R. C. Shah and M. B. Ichaporla, *J. Chem. Soc.*, 431 (1936).

<sup>40</sup> P. Lederer, V. Trcka, S. Hynie, and Z. Budesinsky, *Cesk. Farm.* **24**, 201 (1975) [*CA* **84**, 105533 (1976)].



In the first of a series of new reactions, Meerwein heated *N*-phenylbenzimidoyl chloride (**56**) with acetonitrile and aluminum chloride to obtain 4-methyl-2-phenylquinazoline (see **1**). He postulated that the nitrilium salt (**57**) (not isolated) was the intermediate. Aromatic nitriles could also be used. The imidoyl chloride could be replaced by a mixture of benzanilide and thionyl chloride; other Lewis acids could replace the aluminum chloride. The solvent could be tetrachloroethane, nitrobenzene, or an excess of the nitrile. Best reaction temperatures ranged from 90° to 160°C and yields were usually excellent. Imidate esters, e.g.,  $\text{PhNC(Ph)OEt}$ , could replace the imidoyl chloride.<sup>41</sup>

In the same program, phenyldiazonium tetrafluoroborate was allowed to react with two molecules of a nitrile ( $\text{RCN}$ ) at 20°–50°C to obtain 2,4-disubstituted (phenyl or benzyl) quinazolines in good yields. The nitrilium salt **58** was thought to be the first stage.<sup>41,42</sup> Somewhat similarly, phenyldiazonium tetrafluoroborate reacted with methyl isothiocyanate to give 2,4-di(methylthio)quinazoline.<sup>41</sup>

In further reactions of *N*-phenylbenzimidoyl chloride (**56**), methyl isothiocyanate and stannic chloride, in nitrobenzene at 110°C, gave 2-phenyl-4-methylthioquinazoline in moderate yield; *N*-phenyltrichloroacetimidoyl chloride reacted similarly.<sup>41</sup> Then, in one of the few reactions that produce a *halogenated* pyrimidine ring, the chloride (**56**) with cyanogen bromide and stannic chloride (in nitrobenzene at 150°C) gave 4-bromo-2-phenylquinazoline in excellent yield.<sup>41</sup>

When phenyl isocyanate was heated above 135°C with aluminum chloride, it dimerized to 3-phenylquinazoline-2,4-dione (moderate yield).<sup>43</sup> The reaction proceeded similarly when a high-boiling solvent replaced the salt.<sup>44</sup>

A few examples are known in which the parent ring is heterocyclic, but any  $\pi$ -deficient character must be neutralized by first incorporating electron-releasing groups (e.g.,  $-\text{NH}_2$  or  $-\text{CONH}-$ ) in the starting material. Thus, 3-amino-1-phenylpyrazol-5-one (see **15**) could be converted to 2-phenylpyrazolo[3,4-*d*]pyrimidin-3-one (see **16**) in good yield by heating

<sup>41</sup> H. Meerwein, P. Laasch, R. Mersch, and J. Nentwig, *Chem. Ber.* **89**, 224 (1956); German Patent 1,074,047 (1960) [*CA* **55**, 21152 (1961)].

<sup>42</sup> H. Meerwein, German Patent 1,109,180 (1953) [*CA* **56**, 8726 (1962)].

<sup>43</sup> N. S. Dokunikhin and L. A. Gaeva, *Zh. Obshch. Khim.* **23**, 606 (1953) [*CA* **48**, 7018 (1954)].

<sup>44</sup> N. S. Dokunikhin, *Org. Poluprod. Krasitali*, 148 (1959) [*CA* **55**, 21140 (1961)].

with formamide at 190°C or with trisformamidomethane at 160°C. The aminomethylene derivative **59** is an intermediate.<sup>45</sup> Similarly, 3-amino-1-phenylpyrazole and benzaldehyde urea [ $\text{PhCH}(\text{NHCONH}_2)_2$ ] were converted by refluxing acetic acid to 1,4-diphenyl-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-6-one, and this could readily be dehydrogenated with bromine.<sup>46</sup> Finally, 2,4,6-triaminopyrimidine underwent a Mannich reaction with formaldehyde and benzylamine to furnish 2,4-diamino-6-benzyl-5,6,7,8-tetrahydropyrimidino[4,5-*d*]pyrimidine (see **7**).<sup>47</sup>

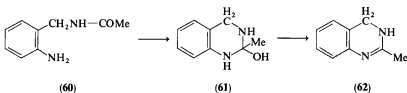
## IV. From Rings with an Amino Group Adjacent to an Aminomethyl, Chloromethyl, or Hydroxymethyl Group

### A. AMINOMETHYL GROUP

As a starting material, 2-aminobenzylamine has two minor disadvantages: it absorbs carbon dioxide rapidly from the air, and the free base (but not the salts) soon polymerizes on storage. The first disadvantage can be overcome by expeditious working and careful storage. The second disadvantage is intensified when electron-releasing substituents are present and diminished by electron-attracting substituents. When an amino and an aminomethyl group are attached to adjacent positions in a  $\pi$ -deficient heterocyclic nucleus, the first disadvantage usually remains, but the second is absent.

#### 1. Reagents: Simple Acylating Agents

When Gabriel and Jansen, in 1890, converted (2-aminobenzyl)acetamide (**60**) to 3,4-dihydro-2-methylquinazoline (**62**) by heating at 240°C, they initiated the most useful of all reactions for making fused 3,4-dihydropyrimidines.<sup>48</sup> These substances are of considerable interest in themselves but



<sup>45</sup> H. Bredereck, F. Effenberger, and W. Resemann, *Chem. Ber.* **95**, 2796 (1962).

<sup>46</sup> V. P. Mamaev and M. A. Mikhaleva, *Khim. Geterosikl. Soedin.* **7**, 535 (1971) [*CA* **76**, 25,244 (1972)].

<sup>47</sup> T. J. Delia and S. M. Sami, *J. Heterocycl. Chem.* **18**, 929 (1981).

<sup>48</sup> S. Gabriel and R. Jansen, *Ber. Dtsch. Chem. Ges.* **23**, 2807 (1890); **24**, 3091 (1891).

are also useful for yielding, by simple oxidation (e.g., with manganese dioxide), fused pyrimidines *unsubstituted* in the 4-position. The most likely course of this reaction is the conversion of **60** to the tetrahedral intermediate **61** (not isolated), which becomes dehydrated to the quinazoline **62**. Yields are usually excellent.

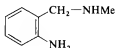
When no substituent is required in the 2-position of the product, milder conditions suffice. Thus, the mere reduction of *o*-nitrobenzylformamide with zinc and hydrochloric acid at 20°C liberated enough energy to give 3,4-dihydroquinazoline directly.<sup>49</sup> Again, 2-amino-4,5-methylenedioxybenzylamine, when refluxed with formic acid and sodium formate for half an hour, yielded 6,7-methylenedioxy-3,4-dihydroquinazoline.<sup>50</sup>

2-Acylaminobenzylamines are another source of 3,4-dihydroquinazolines, which they form by heating in the solid state<sup>48,49,51</sup> or in the presence of an acid<sup>52</sup> (e.g., a mixture of sulfuric acid with acetic anhydride or acetyl chloride for cyclizing 2-acetamidobenzylamine).<sup>53,54</sup>

To obtain an alkyl group in the 1-position of the product, 2-benzylamino-benzylamine was refluxed with formic acid for 45 min to yield 1-benzyl-1,4-dihydroquinazoline (**63**) in excellent yield.<sup>51</sup> Without such an anchoring



(63)



(64)

group in the 1-position, 1,4-dihydroquinazolines tautomerize to the thermodynamically more stable 3,4-dihydroquinazolines. The product obtained by cyclizing 2-acetamidobenzylamine, long supposed<sup>55</sup> to be 2-methyl-1,4-dihydroquinazoline, is now known to be the 3,4-dihydro isomer.<sup>51</sup>

3-Substituted 3,4-dihydroquinazolines were obtained without difficulty by boiling 2-amino-3-(*N*-methyl)benzylamine (**64**) with formic acid.<sup>56</sup>

More severe conditions are required for the Gabriel-Jansen reaction when the starting material is a  $\pi$ -deficient nucleus. Thus, 2-amino-3-amino-methyl-4,6-dimethylpyridine and formic acid needed the dehydrating effect

<sup>49</sup> S. Gabriel, *Ber. Dtsch. Chem. Ges.*, **36**, 800 (1903).

<sup>50</sup> R. Wilkendorf, *Ber. Dtsch. Chem. Ges.*, **52**, 606 (1919).

<sup>51</sup> W. L. F. Armarego, *J. Chem. Soc.*, 2697 (1961).

<sup>52</sup> O. Widman, *J. Prakt. Chem.* [2] **47**, 343 (1893).

<sup>53</sup> W. E. Hanford and R. Adams, *J. Am. Chem. Soc.*, **57**, 921 (1935).

<sup>54</sup> O. Stillich, *Ber. Dtsch. Chem. Ges.*, **36**, 3115 (1903); **38**, 1241 (1905).

<sup>55</sup> A. Bischler, *Ber. Dtsch. Chem. Ges.*, **26**, 1891 (1893).

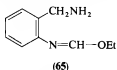
<sup>56</sup> S. Gabriel and J. Colman, *Ber. Dtsch. Chem. Ges.*, **37**, 3643 (1904).



of xylene in a Dean-Stark trap to give a good yield of 5,7-dimethyl-3,4-dihydropyrido[2,3-*d*]pyrimidine (see 3). Similarly, 2-amino-3-acetamido- and 2-amino-3-benzamidomethyl-4,6-dimethylpyridines required the stronger dehydrating effect, of phosphoryl chloride to produce good yields of the methyl (and phenyl) homologs of this pyridopyrimidine.<sup>57</sup> Even these severe conditions may not suffice if the starting nucleus has more than one double-bonded nitrogen atom, and in such cases the use of ortho esters or (better) amidines is necessary.

## 2. Reagents: Ortho Esters

The mechanism of cyclization with ortho esters differs from that of simple acylating agents, such as acetic anhydride, in that the aromatic rather than the aliphatic primary amino group is the first site of attack. The extended conjugation that arises in this way, as in 65 for example, promotes the reaction. Ring closure is aided by the loss of the —OEt group and by its



electron-withdrawing effect, which aids electrophilic attack on the aliphatic amino group.

In the earliest example of this type of reaction,<sup>58</sup> 2-amino-5-methyl(*N*-*p*-tolyl)benzylamine and triethyl orthoformate were heated at 100°C for 1 hr to furnish a good yield of 6-methyl-3-*p*-tolyl-3,4-dihydroquinazoline (see 1).<sup>58</sup> The same authors obtained the 2-methyl homolog by substituting ethyl acetimidate (in boiling benzene) for the ortho ester.

The orthoformate reaction was adapted to deal with  $\pi$ -deficient starting material; an important condition is that the surrounding bath be hot enough (say 145°C) to boil the ortho ester and not merely the ethanol that it produces.<sup>59</sup> Under these conditions, 2-amino-3-aminomethylpyrazine (see 9) gave 3,4-dihydropteridine (see 10) with triethyl orthoformate and the 2-methyl homolog with triethyl orthoacetate; similarly, 2-amino-3-amino-methyl-5-methylpyrazine furnished 6-methyl-3,4-dihydropteridine, all in good yield.<sup>59</sup>

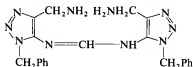
Starting materials that have nuclei more  $\pi$ -deficient than pyrazine must be converted to cations before they can react with ortho esters. These salts

<sup>57</sup> P. J. Vanderhorst and C. S. Hamilton, *J. Am. Chem. Soc.*, **75**, 656 (1953).

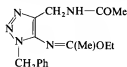
<sup>58</sup> R. Walther and R. Bamberg, *J. Prakt. Chem.*, [2] **73**, 209 (1906).

<sup>59</sup> A. Albert and K. Ohta, *J. Chem. Soc. C*, 1540 (1970).

act as a source of hydrogen ions that provide intermediates of type **65** with a better leaving group, namely,  $\text{—EtOH}^+$  in place of  $\text{—EtO}$ .<sup>60</sup> Thus, 4-amino-5-aminomethyl-3-benzyl-1,2,3-triazole (see **20**), which did not react with triethyl orthoformate at  $145^\circ\text{C}$ , did so at  $100^\circ\text{C}$  if first made into the hydrochloride, giving an excellent yield of 9-benzyl-1,6-dihydro-8-azapurine (see **21**). The corresponding acetate gave exclusively *N,N'*-bis(5-aminomethyl-3-benzyl-1,2,3-triazol-4-yl)formamidine (**66**). Paradoxically, in the condensa-



(66)



(67)

tion of the same triazole with triethyl orthoacetate, the acetate of the starting material gave 9-benzyl-1,6-dihydro-2-methyl-8-azapurine (good yield), whereas the hydrochloride produced exclusively 5-acetamidomethyl-3-benzyl-4-(ethoxymethyleneamino)-1,2,3-triazole (**67**), which resisted cyclization. The free base of the starting material was converted to the lower homolog (4-ethoxymethyleneamino) of **67** when boiled with triethyl orthoformate and acetic anhydride.<sup>60</sup> The unpredictable nature of the conditions needed to produce fused pyrimidines from highly  $\pi$ -deficient nuclei and ortho esters has led to amidines replacing the latter (see next section).

However, ortho esters have proved ideal for cyclizing alicyclic diamines. For example, *trans*-1-amino-2-aminomethylcyclohexane, refluxed with triethyl orthoformate, cooled, and acidified, gave *trans*-3,4,4a,5,6,7,8,8a-octa-hydroquinazoline (see **1**) in excellent yield; the *cis* isomer behaved similarly.<sup>61</sup>

### 3. Reagents: Amidines

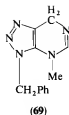
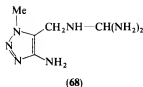
In the first use of an amidine for this type of synthesis, 2-amino-5-methyl-*N*-*p*-tolylbenzylamine was heated with *N,N'*-diphenylformamidine at  $100^\circ\text{C}$  to give 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline (see **1**) (excellent yield) and two molecular proportions of aniline.<sup>62</sup>

In a more direct attack, 4-amino-5-aminomethyl-1-methyl-1,2,3-triazole (see **20**) was refluxed with a suspension of formamidine acetate; a quantitative yield of 7-methyl-1,6-dihydro-8-azapurine (see **21**) was obtained.<sup>60</sup> The presumed intermediate (**68**) was not isolated (but see ref. 63).

<sup>60</sup> A. Albert, *J. C. S. Perkin I*, 291 (1976).

<sup>61</sup> W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc. C*, 238 (1971).

<sup>62</sup> E. C. Wagner, *J. Org. Chem.* **5**, 133 (1940).



This reaction was extended to the 2-methyl and 3-benzyl analogs of the starting material, making use of formamidine, acetamidine, and trichloroacetamidine. Butanol proved to be the best solvent, and condensation times from 1 to 4 hr gave good to excellent yields. Neither the free bases nor the hydrochlorides of the amidines gave much product. It was thought that the free amidines were rather unstable under the conditions of the reaction and that the acetates furnished a steady supply of them.<sup>60</sup>

Steric hindrance was encountered in applying this reaction to the synthesis of 1- and 3-methyl-8-azapurines. Thus, 4-amino-3-benzyl-5-methylamino-methyl-1,2,3-triazole reacted so slowly with formamidine acetate in boiling butanol that the amidine underwent destruction; this situation was remedied by feeding in new supplies of the amidine every 2 hr, giving an excellent yield of 9-benzyl-1,6-dihydro-1-methyl-8-azapurine.<sup>63</sup>

Under these conditions, the even less reactive 5-aminomethyl-3-benzyl-4-methylamino-1,2,3-triazole gave some of the 5-formamidomethyl analog, but no 9-benzyl-3,6-dihydro-3-methyl-8-azapurine (69). An attempt to cyclize this formyl derivative by heating at 200°C caused it to undergo a Dimroth retrogression to 4-benzylamino-5-formamidomethyl-3-methyl-1,2,3-triazole; other attempts to close the ring also failed.<sup>64</sup>

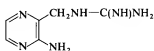
#### 4. Reagents: Guanidine, Cyanogen Bromide, or *S*-Methylisothiurea

In recent years, several methods have been introduced for obtaining a (fused) dihydropyrimidine ring that has a basic group in the 2-position. Thus, 2-amino-3-aminomethylpyrazine was condensed with *S*-methylisothiuronium chloride in boiling ethanol to give 2-amino-3-guanidinomethylpyrazine (70), which was converted to 2-amino-3,4-dihydropteridine (see 10) when refluxed with ethanolic sodium ethoxide, all in good overall yield<sup>59</sup> (see ref. 63 for an example from the 1,2,3-triazole series). When the nucleus is not  $\pi$ -deficient, the reaction goes faster and ring closure is immediate. Thus,

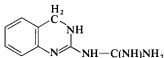
<sup>63</sup> A. Albert, *J. C. S. Perkin I*, 513 (1978).

<sup>64</sup> A. Albert, *J. C. S. Perkin I*, 2344 (1981).

excellent yields of 3,4,4a,5,6,7,8,8a-octahydroquinazoline were obtained by boiling 1-amino-2-aminomethylcyclohexane and *S*-methylisothiuronium sulfate in water; the *cis* and *trans* isomers were made in this way, each of them as (–)- and (+)-enantiomers.<sup>61,65</sup>



(70)



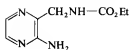
(71)

A similar reaction was accomplished with cyanogen bromide. When the appropriate *N*-alkyl-4-amino-5-aminomethyl-1,2,3-triazoles were refluxed with cyanogen bromide in methanol, 2-amino-1-methyl-, 2-methyl-, and 3-benzyltriazoles were obtained in 40–75% yields.<sup>66</sup>

2-Aminobenzylamine and dicyanamide, boiled in water, produced 2-guanidino-3,4-dihydroquinazoline (71).<sup>67</sup>

### 5. Reagents: Ethyl Chloroformate, Phosgene, or Carbon Disulfide

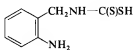
These reactions provide reliable pathways to (fused) dihydropyrimidines bearing an oxygen or a sulfur atom in the 2-position. Thus, 2-amino-3-aminomethylpyrazine and ethyl chloroformate, in chloroform containing some triethylamine, gave 2-amino-3-ethoxycarbonyl aminomethylpyrazine (72), which was converted to 3,4-dihydropteridin-2-one (73) in good overall yield when refluxed with ethanolic sodium ethoxide.<sup>59</sup> Similarly, the appropriate *N*-alkyl-4-amino-5-ethoxycarbonylaminoethyl-1,2,3-triazoles (see 20), when refluxed in butanolic sodium butoxide, gave 51–85% yields of 7-methyl-, 8-methyl-, and 9-benzyl-1,6-dihydro-8-azapurin-2-ones (see 21).<sup>66</sup> Again, 2-amino-3-ethoxycarbonylaminoethyl-4,6-dimethylpyridine, refluxed with diphenyl ether (70 min), gave an excellent yield of 5,7-dimethyl-3,4-dihydropyrido[2,3-*d*]pyrimidin-2-one (see 3).<sup>57</sup>



(72)



(73)



(74)



(75)

<sup>65</sup> W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc. C*, 1597 (1970).

<sup>66</sup> A. Albert, *J. C. S. Perkin I*, 2918 (1980).

<sup>67</sup> L. Doub, L. M. Richardson, and A. Campbell, German Patent 1,139,124 (1962) [*CA* 58, 9100 (1963)].

The historical origin of this reaction is the use of phosgene on 2-aminobenzylamines to prepare 3,4-dihydroquinazolin-2-ones.<sup>58,68</sup> In a more recent example of the use of this reagent, a solution of it in chloroform was stirred with one of *trans*-1-amino-2-aminomethylcyclohexane in aqueous alkali for 3 days at 20°C, producing an excellent yield of *trans*-3,4,4a,5,6,7,8,8a-octahydroquinazolin-2-one (the ethyl chloroformate approach was first attempted, but the intermediate urethane could not be cyclized).<sup>61</sup> When carbon disulfide replaced the phosgene and alkali, the corresponding 2-thione was produced in excellent yield.<sup>61</sup>

The use of carbon disulfide dates from 1895, when Busch condensed 2-aminobenzylamine with this reagent in boiling ethanolic sodium ethoxide to give 3,4-dihydroquinazoline-2-thiones.<sup>68</sup> This procedure was also suitable for 2-amino-*N*-alkyl- and -arylbenzylamines. When ammonia replaced the stronger base, the intermediate dithiocarbamate (**74**) was isolated; in the absence of base, a salt of **74** with the original diamine was obtained. As is usual with carbon disulfide, the aliphatic rather than the aromatic amino group is preferentially attacked.<sup>68</sup>

The Busch synthesis works well with many  $\pi$ -deficient nuclei. Thus, quantitative yields of 7- and 8-methyl-1,6-dihydro-8-azapurine-2-thiones (see **21**) were obtained by heating the corresponding 1,2,3-triazole derivatives with carbon disulfide in pyridine containing a little triethylamine for 6 hr at 115°C.<sup>69</sup> However, a 3-methyl- and 3-benzyl-4-amino-5-aminomethyl-1,2,3-triazoles produced only 3-alkyl-3,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]-thiazine-5-thiones (**75**). It was thought that the Busch reaction was slowed by the neighboring 3-alkyl groups and that this allowed the faster N  $\rightarrow$  S migration of the methylene group in the dithiocarbamate intermediate, similar to **74**, a process that was followed by <sup>1</sup>H NMR; ring closure to **75** then followed.<sup>70</sup>

Another unusual closure led to the production of 8-aminoimidazo-[1,5-*a*]pyrazine-3-thiol (**76**) from 2-amino-3-aminomethylpyrazine (see **9**) and carbon disulfide in pyridine.<sup>59</sup>

## 6. Reagents: Oxalic Acid Derivatives

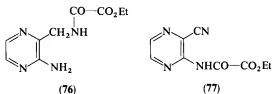
Derivatives of oxalic acid should yield (fused) dihydropyrimidines substituted by a carboxylic acid derivative in the 2-position, but the reaction has been little explored. 2-Amino-3-ethoxalylaminomethylpyrazine (**76**) resisted

<sup>68</sup> M. Busch, *J. Prakt. Chem.* [2] **51**, 113, 257; R. E. Orth and J. W. Jones, *J. Pharm. Sci.* **50**, 866 (1961).

<sup>69</sup> A. Albert, *J. C. S. Perkin I*, 887 (1981).

<sup>70</sup> A. Albert, *J. C. S. Perkin I*, 2009 (1980).

cyclization with such likely reagents as phosphoryl chloride in hot pyridine, and ethanolic sodium ethoxide. However, 2-ethoxalylaminopyrazine-3-carbonitrile (77) (from 2-amino-3-cyanopyrazine and ethoxalyl chloride) gave a low yield of ethyl 3,4-dihydropteridine-2-carboxylate (see 10) when hydrogenated over Raney nickel.<sup>59</sup>



Similar attempts to cyclize 4-amino-3-benzyl- or 4-amino-1-methyl-5-ethoxalylaminomethyl-1,2,3-triazole (see 20) were unsuccessful. Surprisingly, 5-aminomethyl-3-benzyl- and 5-aminomethyl-1-methyl-4-oxamoylamino-1,2,3-triazoles spontaneously isomerized to 4-amino-3-benzyl- and 4-amino-1-methyl-5-oxamoylamino-1,2,3-triazoles, which resisted ring closure with stannic chloride, phosphoryl chloride, or boiling butanolic sodium butoxide.<sup>69</sup>

### 7. Reagents: Aldehydes

The use of aldehydes to make (fused) tetrahydropyrimidines was initiated in 1896 by Busch, who slowly added aqueous formaldehyde to an aqueous solution of 2-aminobenzylamine. The precipitate (an intermediate) was converted to 1,2,3,4-tetrahydroquinazoline (see 1) with ethanolic hydrogen chloride (no yield given).<sup>71</sup> 3-Phenyltetrahydroquinazoline was made by adding formaldehyde to 2-amino-*N*-phenylbenzylamine in ethanol containing potassium hydroxide.<sup>71</sup> Without recourse to acidic or basic catalyst, all four stereoisomers of decahydroquinazoline were obtained in excellent yields by stirring the appropriate stereoisomer of 1-amino-2-aminomethylcyclohexane with aqueous formaldehyde at 20°C.<sup>65</sup>

Turning to the  $\pi$ -deficient nuclei, we see that 2-amino-3-aminomethylpyrazine (see 9) and formaldehyde, in boiling 5 *N* sodium hydroxide, gave a moderate yield of 1,2,3,4-tetrahydropteridine (see 10) in 5 min.<sup>59</sup> 4-Amino-5-aminomethyl-2-methylpyrimidine (see 2), when condensed with 4-methoxy- and 4-nitrobenzaldehydes in boiling benzene (a Dean-Stark trap was used), furnished excellent yields of 7-aryl-2-methyl-5,6,7,8-tetrahydropyrimidino-[4,5-*d*]pyrimidine (see 7). However *p*-chlorobenzaldehyde did not carry the

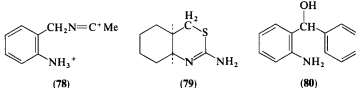
<sup>71</sup> M. Busch, *J. Prakt. Chem.* [2] 53, 414 (1896); M. Busch, R. Birk, and W. Lehrmann, *ibid.* 55, 356 (1897).

reaction past the Schiff base (on the aminomethyl group) stage. This anil was reduced with sodium borohydride to give 4-amino-5-(*p*-chlorobenzylamino-methyl)pyrimidine, which, when cyclized with acetaldehyde in boiling benzene containing a trace of acid, produced a good yield of 2,7-dimethyl-6-(*p*-chlorobenzyl)-5,6,7,8-tetrahydropyrimidino[4,5-*d*]pyrimidine.<sup>72</sup>

The Schiff bases, supposedly formed from the reaction of 2-amino-3-aminomethyl-6-methylpyridine and benzaldehyde (also other aromatic aldehydes) in methanolic sodium methoxide,<sup>73</sup> may be 1,2,3,4-tetrahydroprido[2,3-*d*]pyrimidines (see 3).<sup>3,72</sup>

## B. CHLOROMETHYL OR HYDROXYMETHYL GROUP

2-(Chloromethyl)aniline hydrochloride reacts at 160°C with the stannic chloride complex of acetonitrile to give 2-methyl-3,4-dihydroquinazoline (see 1). The nitrilium salt 78 is presumed to be the intermediate. Yields were excellent when other aliphatic and aromatic nitriles were used. *N*-Methyl-2-(chloromethyl)aniline gave 2-alkyl- or 2-aryl-1,4-dihydroquinazolines in excellent yields.<sup>74</sup>



In an attempt to make octahydroquinazoline-2-thione, *cis*-2-bromomethylcyclohexylamine was fused with thiourea at 155°C for 3 hr, but only *cis*-2-amino-4a,5,6,7,8,8a-hexahydro-4*H*-1,3-benzothiazine (79) could be isolated (good yield). Aqueous thiocyanic acid gave the same product (low yield). Aqueous cyanic acid furnished the corresponding aminobenzoxazine (excellent yield), whereas fusion with guanidine carbonate at 120°C furnished *cis*-4a,5,6,7,8,8a-hexahydrobenzoxazin-2-one (good yield).<sup>61</sup>

2-Aminobenzyl alcohol and aqueous cyanic acid gave 2-ureidobenzyl alcohol, which, when briefly heated with dilute acid, gave 3,4-dihydroquinazolin-2-one. Similarly, 2-aminobenzyl alcohol and allyl isothiocyanate produced, in two steps, 3-allyl-3,4-dihydroquinazoline-2-thione (no yields given).<sup>75</sup> 2-Aminobenzhydryl (80) and aqueous thiocyanic acid, when briefly heated on a water bath, gave 4-phenyl-3,4-dihydroquinazoline-2-

<sup>72</sup> R. E. Harmon, J. L. Parsons, and S. K. Gupta, *J. Org. Chem.* **34**, 2760 (1969).

<sup>73</sup> H. Suter, E. Habricht, and H. Martin, Swiss Patent 331,989 (1958) [*CA* **53**, 5292 (1959)].

<sup>74</sup> M. Lora-Tamayo, R. Madroñero, and G. Garcia-Muñoz, *Chem. Ber.* **94**, 208 (1961).

<sup>75</sup> H. Söderbaum and O. Widman, *Ber. Dtsch. Chem. Ges.* **22**, 1665 (1889).

thione. The same starting material, fused with urea (at 175°C for 45 min), produced 4-phenyl-3,4-dihydroquinazolin-2-one (no yield).<sup>76</sup> 2-Amino-phenyl-*p*-tolylcarbinol, fused with urea at 185°C, gave a good yield of 4-*p*-tolyl-3,4-dihydroquinazolin-2-one, and aqueous thiocyanic acid produced the analogous 2-thione.<sup>77</sup> (For other, similar reactions see ref. 78). 2-Aminobenzhydrol and aqueous cyanic acid formed 2-ureidobenzhydrol, which cold 10 *N* hydrochloric acid converted to 4-phenyl-3,4-dihydroquinazolin-2-one (excellent yield).<sup>79</sup>

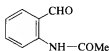
## V. From Rings with an Amino Group Adjacent to an Aldehyde or Ketone Group

Essentially, the aldehydes produce (fused) pyrimidines that are unsubstituted in the 4-position, whereas the ketones provide an alkyl or aryl group in this place.

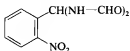
### A. FROM AMINOALDEHYDES

This synthesis was first described by Bischler, who, in 1891, prepared 2-methylquinazoline by heating 2-acetamidobenzaldehyde (**81**) with ethanolic ammonia at 100°C.<sup>80</sup> It is now known that the reaction proceeds excellently at room temperature, being complete in 18 hr (in even less time when the acyl group is more electron attracting).<sup>81</sup> Precautions to avoid polymerization of 2-aminobenzaldehyde when it is being acylated have been worked out.<sup>81</sup>

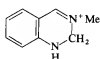
An alternative approach, when the appropriate 2-nitrobenzaldehyde is available, is Riedel's synthesis<sup>82</sup>; dry hydrogen chloride was passed through a suspension of the aldehyde in formamide to give (**82**), which was reduced



(81)



(82)



(83)

<sup>76</sup> S. Gabriel and R. Stelzner, *Ber. Dtsch. Chem. Ges.* **29**, 1300 (1896).

<sup>77</sup> H. Kippenberg, *Ber. Dtsch. Chem. Ges.* **30**, 1130 (1897).

<sup>78</sup> A. Drawert, *Ber. Dtsch. Chem. Ges.* **32**, 1259 (1899), G. Hanschk, *ibid.*, 2021.

<sup>79</sup> R. T. Puckowski and W. A. Ross, *J. Chem. Soc.*, 3555 (1959).

<sup>80</sup> A. Bischler, *Ber. Dtsch. Chem. Ges.* **24**, 506 (1891).

<sup>81</sup> W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc. C*, 234 (1966).

<sup>82</sup> J. D. Riedel, German Patent 174,941 (1905) [*Chem. Zentralbl.* **II**, 1372 (1906)].



with zinc and acetic acid to quinazoline. The reaction was extended to substituted 2-nitrobenzaldehydes in good to excellent yields.<sup>83</sup> Other aliphatic (but not aromatic) amides can replace formamide, but the reaction did not work with 2-nitroacetophenone.

The rarity of 1,2-dihydroquinazolines lends interest to the preparation of 3-methyl-1,2-dihydroquinazolinium (**83**), isolated as its picrate, from a mixture of 2-aminobenzaldehyde, formaldehyde, and methylamine set aside at 20°C at pH 5 for 3 days (excellent yield).<sup>84</sup>

$\pi$ -Deficiency in an original ring makes the reaction more stubborn. Thus, 2-formamido-3-formylpyridine required heating at 100°C with methanolic ammonia to give a good yield of 1,3,8-triazanaphthalene (see **3**), and 4-formamido-3-formylpyridine reacted yet more reluctantly.<sup>85</sup> When still more  $\pi$ -deficiency is present, even the preliminary acylation becomes reluctant. Thus, 2-aminopyrazine-3-aldehyde resisted acetylation until converted to its acetal; hydrolysis of the acetal group furnished 2-acetamidopyrazine-3-aldehyde, which was converted to 2-methylpteridine (see **10**) with cold ethanolic ammonia, but in only moderate yield. A good yield of pterid-2-one was obtained by using ethyl chloroformate as the acylating agent in this acetal procedure, but several other acylating agents failed.<sup>86</sup>

In the still more  $\pi$ -deficient 1,2,3-triazole series (see **20**), several 4-amino-5-formyl derivatives resisted both direct acylation and acetal formation. A successful alternative was to form intermediates with side chains conjugated to the nucleus. For example, 1- and 2-methyl-, as well as 3-benzyl-4-amino-1,2,3-triazole-5-aldehydes reacted with a cold mixture of dimethylformamide and phosphoryl chloride to give excellent yields of, e.g., 3-benzyl-4-dimethylaminomethyleneamino-1,2,3-triazole-5-aldehyde (**84**). This was converted to 9-benzyl-8-azapurine (see **21**) in excellent yield by refluxing in methanolic ammonium acetate.<sup>87</sup> In a variation of this reaction, an imide (**85**) replaced the amine (**84**) as intermediate. Thus, 4-amino-1-methyl-1,2,3-triazole-5-aldehyde and triethyl orthoacetate, refluxed for 2 hr, gave an excellent yield of 4-ethoxyethylideneamino-1,2,3-triazole-5-aldehyde (**85**), cyclized, by stirring in cold ethanolic ammonia, to 2,7-dimethyl-8-azapurine (good yield).<sup>87</sup>

In an extension of these reactions, 4-amino-2-methyl-1,2,3-triazole-5-aldehyde was refluxed with tetraethyl orthocarbonate. The isolated intermediate (**86**), stirred with cold ethanolic ammonia, provided 2-ethoxy-8-methyl-8-azapurine in good yield.<sup>87</sup> This reaction seems to be unique for producing a 2-alkoxy-substituted pyrimidine ring.

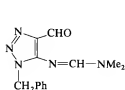
<sup>83</sup> W. L. F. Armarego, *J. Chem. Soc.*, 561 (1962).

<sup>84</sup> C. Schöpf and F. Oechler, *Justus Liebigs Ann. Chem.*, **523**, 1 (1936).

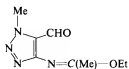
<sup>85</sup> W. L. F. Armarego, *J. Chem. Soc.*, 4094 (1962).

<sup>86</sup> A. Albert and K. Ohta, *J. Chem. Soc. C*, 2357 (1971).

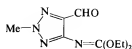
<sup>87</sup> A. Albert and H. Taguchi, *J. C. S. Perkin I*, 2037 (1973).



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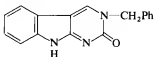
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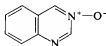
(86)

Bischler's reaction was modified to introduce polar groups into the 2-position of the product. Thus, 2-aminobenzaldehyde gave 2-aminoquinazoline quantitatively when heated with guanidine nitrate and sodium carbonate in decalin for 30 min.<sup>88</sup> Similarly, several methoxy derivatives of 2-aminobenzaldehyde gave the corresponding methoxyquinazolines in low to moderate yields.<sup>89</sup> A curious reductive loss of the methylthio group occurred when 4-amino-5-formyl-6-methylthiopyrimidine was boiled with formamidine acetate in ethoxyethanol for 20 mins, giving a moderate yield of 4-aminopyrimidino[4,5-*d*]pyrimidine (see 7).<sup>90</sup>

Quinazolin-2-one was obtained quantitatively by fusing 2-aminobenzaldehyde with urea (10 min at 150°C).<sup>76,91</sup> Similarly, 2-amino-3-formylpyridine and urea (15 min at 160°C) gave an excellent yield of pyrido[2,3-*d*]pyrimidin-2-one (see 3).<sup>92</sup> Finally, as an example from  $\pi$ -excessive chemistry, 2-aminoindole-3-aldehyde was converted to its 2-benzoyloxycarbonyl derivative, which benzylamine quantitatively converted to 3-benzyl-9*H*-pyrimidino[4,5-*b*]indol-2-one (87)<sup>93</sup>



(87)



(88)

The oximes of aminoaldehydes yield the N-3 oxides of (fused) pyrimidines. Thus, several methoxy derivatives of *trans*-2-aminobenzaldoximes, heated at 140°C in triethyl orthoformate, gave good yields of the corresponding methoxy derivatives of quinazoline 3-oxide (88). Ultraviolet light rearranged these products to quinazolin-4-ones. (The *cis* forms of these aldehydes produced only benzoxadiazepines.) The same aldehydes, heated in decalin with

<sup>88</sup> H. Rodda, *J. Chem. Soc.*, 3509 (1956).

<sup>89</sup> K. Tsuda, S. Ikuma, M. Kawamura, R. Tachikawa, Y. Baba, and T. Miyadera, *Chem. Pharm. Bull.* **10**, 856 (1962).

<sup>90</sup> E. C. Taylor and W. A. Ehrhart, *J. Am. Chem. Soc.* **82**, 3138 (1960).

<sup>91</sup> S. Gabriel and T. Posner, *Ber. Dtsch. Chem. Ges.* **28**, 1029 (1895).

<sup>92</sup> A. Albert and F. Reich, *J. Chem. Soc.*, 1370 (1960).

<sup>93</sup> Y. Sato, T. Tanaka, and T. Nagasaki, *Yakugaku Zasshi* **90**, 618 (1970) [*CA* **73**, 35318 (1970)].

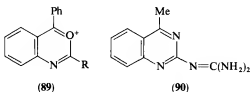
guanidine carbonate, lost the N-bonded oxygen atom at some stage and gave good yields of the 5-, 6-, and 7-methoxy derivatives of 2-aminoquinazolines. The corresponding *cis*-aldehydes did not react.<sup>94</sup>

2-Aminobenzaldoxime and aryl isothiocyanates, in ethanol at room temperature, produced 3-aryl-4-ethoxy-3,4-dihydroquinazoline-2-thiones (see 1).<sup>95</sup>

## B. FROM AMINO KETONES

Soon after he had discovered his synthesis of quinazolines from aminoaldehydes, Bischler turned to the amino ketones to obtain quinazolines with alkyl or aryl substituents in the 4-position (see 1). He showed that *N*-acyl derivatives of 2-aminobenzophenone, heated at 170°C with ethanolic ammonia, furnished 4-phenylquinazolines,<sup>96</sup> and 2-aminoacetophenone behaved similarly.<sup>97</sup> However, it was later found that such severe conditions were unnecessary, for 4-methylquinazoline was produced quantitatively from 2-formamidoacetophenone and ethanolic ammonia at 20°C in 18 hr, and 2,4-dimethylquinazoline was similarly prepared (from 2-acetamidoacetophenone) in 5 days.<sup>81</sup>

In an alternative approach, ammonia was bubbled through molten ammonium acetate containing 2-formamidoacetophenone at 160°C to give an excellent yield of 4-methylquinazoline.<sup>98</sup> In a ring transformation, ammonia was used to convert 2-alkyl-4-phenyl-3,1-benzoxazinium (89) salts to 2-alkyl-4-phenylquinazolines.<sup>99</sup>



Several reactions have been devised to obtain a product with a polar group in the 2-position. Thus, 2-aminoacetophenone gave 2-amino-4-methylquinazoline with cyanamide, 2-cyanamino-4-methylquinazoline with sodium dicyanamide, and 2-guanidino-4-methylquinazoline (90) with di-

<sup>94</sup> D. J. Brown and B. T. England, *Isr. J. Chem.* **6**, 569 (1968).

<sup>95</sup> C. V. Gheorghiu, *J. Prakt. Chem.* [2] **130**, 49 (1931); *Bull. Soc. Chim. Fr.* [5] **2**, 223 (1935).

<sup>96</sup> A. Bischler and D. Barad, *Ber. Dtsch. Chem. Ges.* **25**, 3080 (1892).

<sup>97</sup> A. Bischler and M. Lang, *Ber. Dtsch. Chem. Ges.* **28**, 279 (1895).

<sup>98</sup> K. Schofield, T. Swain, and R. S. Theobald, *J. Chem. Soc.*, 1924 (1952).

<sup>99</sup> V. I. Dulenko, N. N. Alexseev, and V. M. Golyak, *Khim. Geterosikl. Soedin.*, 1286 (1976).

cyandiamide [NCNHC(NH)NH<sub>2</sub>] in good, moderate, and excellent yields, respectively.<sup>100</sup>

Fusion of 2-aminobenzophenones with urea (1 hr at 200°C) produced excellent yields of 4-phenylquinazolin-2-ones. Vigorous stirring was essential to overcome frothing in this highly exothermic reaction.<sup>101</sup> However, 2-aminoacetophenone gave only a charred mass; it was better to react it with ethyl chloroformate and cyclize the urethane with ethanolic ammonia at 110°C (excellent yield).<sup>81</sup> In a redox-type reaction, in which an ethyl group is lost as acetaldehyde, fusion of 3-benzoyl-4-diethylaminopyrrole (2 hr at 200°C) with urea gave 1-ethyl-4-phenylpyrrolo[3,4-*d*]pyrimidin-2-one (see 13).<sup>102</sup>

Other reagents are available for introducing the 2-oxo group. Thus, 2-amino-3-pyridyl phenyl ketone, ethyl carbamate, and zinc chloride, fused for 45 min at 230°C, gave a good yield of 4-phenylpyrido[2,3-*d*]pyrimidin-2-one (see 3). In addition, 2-*tert*-butylamino-3-pyridylphenylketonimine, phosgene, and triethylamine, stirred in cold benzene for 10 min, produced 1-*tert*-butylamino-4-phenylpyrido[2,3-*d*]pyrimidin-2-one in good yield.<sup>103</sup> 2-Amino-5-chlorobenzophenone and methyl isocyanate, refluxed 15 hr in dichloromethane, gave an excellent yield of 6-chloro-3-methyl-4-phenylquinazolin-2-one; methyl isothiocyanate in ethanol furnished the corresponding 2-thione.<sup>104</sup>

2-Aminobenzophenone and methyl isothiocyanate, set aside at 20°C for several days, gave 3-methyl-4-hydroxy-4-phenyl-3,4-dihydroquinazoline-2-thione (**91a**) (no yield given).<sup>105</sup> A similar compound (**91b**) was formed by boiling a solution of isatin in aqueous sodium hydroxide (actually sodium isatinate, **92**) with phenyl isothiocyanate. Refluxing in benzene effected decarboxylation to **91c**, the molecular weight of which was checked. It turned out to be stable but could be dehydrated to 3-phenylquinazoline-2-thione by more severe heating. The latter compound readily added ethanol and other nucleophiles across the 3,4-double bond (no yields given in this paper).<sup>106</sup>

Several other reactions of isatin derivatives will now be described. Isatin-2-oxime (**93**) underwent a Beckmann-like rearrangement to quinazoline-2,4-dione when heated with dilute sodium hydroxide (no yield given).<sup>107</sup>

<sup>100</sup> L. F. Theiling and R. L. McKee, *J. Am. Chem. Soc.*, **74**, 1834 (1952); S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962).

<sup>101</sup> K. Schofield, *J. Chem. Soc.*, 1927 (1952).

<sup>102</sup> G. Tarzia and G. Panzone, *Gazz. Chim. Ital.*, **108**, 591 (1978).

<sup>103</sup> G. E. Hardtmann, B. Huegi, G. Koletar, S. Kroin, H. Ott, J. W. Perrine, and E. I. Takesue, *J. Med. Chem.*, **17**, 636 (1974).

<sup>104</sup> W. Metlesics, G. Silverman, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **31**, 1007 (1966).

<sup>105</sup> C. V. Gheorghiu and B. Arventi, *Bull. Soc. Chim. Fr.*, [5] **5**, 38 (1938).

<sup>106</sup> A. Reissert and H. Schaaf, *Ber. Dtsch. Chem. Ges.*, **59**, 2494 (1926).

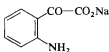
<sup>107</sup> G. Heller, *Ber. Dtsch. Chem. Ges.*, **49**, 2757 (1916).



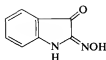
(91a) X = Ph; R = Me

(91b) X = CO<sub>2</sub>H; R = Ph

(91c) X = H; R = Ph



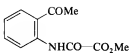
(92)



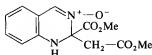
(93)



(94)



(95)



(96)

3-Arylimino derivatives (94) of isatin were converted by alkaline hydrogen peroxide to 3-arylquinazoline-2,4-diones in good yield.<sup>108</sup> *N*-Acetyl-5-methylisatinic acid, heated for 2 hr "not above 120°C" gave 2,6-dimethylmethylisatinic acid, heated for 2 hr "not above 120°C" gave 2,6-dimethylquinazoline-4-carboxylic acid (no yield given).<sup>109</sup> Similarly, *N*-benzoylisatinic acid gave a good yield of 2-phenylquinazoline-4-carboxylic acid.<sup>110</sup> *N*-Formylisatinic acid similarly provided quinazoline-4-carboxylic acid, and *N*-formylisatin gave quinazoline-4-carboxamide, both in excellent yields.<sup>111</sup> Isatinic acid produced 4-amino- and 2-oxoquinazoline-4-carboxylic acids with guanidine and urea, respectively, both in excellent yields.<sup>112</sup>

2-Methoxalylamidoacetophenone (95) and ethanolic ammonia (5 hr at 150°C) gave 4-methylquinazoline-2-carboxamide (good yield).<sup>110</sup>

Some reactions that produce quinazoline 3-oxides will now be described. 2-Aminoacetophenone oxime, heated with triethyl orthoformate, provided 4-methyl-1,2-dihydroquinazoline 3-oxide.<sup>113</sup> The same oxime, in acetone at 20°C, gave 2,2,4-trimethylquinazoline 3-oxide but, when methazonic acid (NO<sub>2</sub>CH<sub>2</sub>CHNOH) was also present, the product was 4-methyl-2-nitromethylquinazoline 3-oxide.<sup>114</sup> 5-Bromo-2-acetamidoacetophenone oxime, boiled with dilute acid, was converted to 2,4-dimethylquinazoline 3-oxide, whereas 2-aminoacetophenone oxime, reacting with benzaldehyde at 20°C,

<sup>108</sup> G. Jacini, *Gazz. Chim. Ital.* **73**, 85 (1943).

<sup>109</sup> A. Bischler and H. P. Muntendam, *Ber. Dtsch. Chem. Ges.* **28**, 723 (1895).

<sup>110</sup> M. T. Bogert and F. P. Nabenbauer, *J. Am. Chem. Soc.* **46**, 1702 (1924).

<sup>111</sup> W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc. B* p. 449 (1967).

<sup>112</sup> G. Stefanović, L. Lorenc, and M. L. Mihailović, *Recl. Trav. Chim. Pays-Bas* **80**, 149 (1961).

<sup>113</sup> K. Adachi, *J. Pharm. Soc. Jpn.* **77**, 507 (1957).

<sup>114</sup> W. L. F. Armarego, T. Batterham, K. Schofield, and R. S. Theobald, *J. Chem. Soc. C*, 1435 (1966).

gave 4-methyl-2-phenyl-1,2-dihydroquinazoline 3-oxide (excellent yields).<sup>115</sup> No proof of 1,2-orientation was given for the dihydro function, and the 1,4-position may be thermodynamically preferred (see ref. 51).

2-Amino-5-chlorobenzophenone oxime, stirred at 20°C with dimethyl acetylenedicarboxylate, gave a good yield of the dimethyl ester of 2-carboxy-6-chloro-1,2-dihydro-4-phenylquinazolin-2-acetic acid (96).<sup>116</sup>

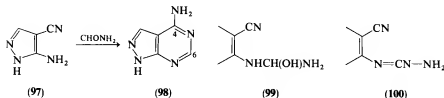
## VI. From Rings with an Amino Group Adjacent to a Nitrile Group

The use of *o*-aminonitriles for the synthesis of fused pyrimidines is of comparatively recent origin. Because this reaction is described, with many tables of examples, in a 1970 monograph,<sup>4</sup> the following account has been confined to essential information, but brought up to date.

### A. REACTIONS THAT GIVE 4-AMINOPYRIMIDINES

#### 1. With Amides, Imidates, or Nitriles

The use of formamide, which was introduced in 1956,<sup>117-119</sup> is exemplified by the conversion of 3-amino-4-cyanopyrazole (97) to 4-aminopyrazolo-[3,4-*d*]pyrimidine (98) in good yield by "boiling" with formamide for 30 min.<sup>118</sup> The product was conveniently obtained by diluting the cooled mass with water. Here, as in most other applications of the reaction, the temperature is not specified. This introduces uncertainty, because formamide vigorously expels bubbles of ammonia and carbon monoxide at about 200°–210°C, decomposing rather than boiling. An addition of acetic anhydride to improve yields has been suggested.<sup>120</sup>



<sup>115</sup> A. Kövendi and M. Kircz, *Chem. Ber.* **98**, 1049.

<sup>116</sup> J. B. Hester, *J. Org. Chem.* **39**, 2137 (1974).

<sup>117</sup> E. C. Taylor and N. W. Kalenda, *J. Am. Chem. Soc.* **78**, 5108 (1956).

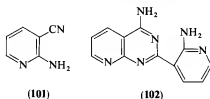
<sup>118</sup> R. K. Robins, *J. Am. Chem. Soc.* **78**, 784 (1956).

<sup>119</sup> C. C. Cheng and R. K. Robins, *J. Org. Chem.* **21**, 1240 (1956).

<sup>120</sup> K. Gewald, *Chem. Ber.* **99**, 1002 (1966).

The product is usually accompanied by a mixture of by-products and starting material. The desired reaction, which a  $\pi$ -deficient nucleus favors, is addition of the amino group of the base across the  $C^+-O^-$  bond of the formamide to give the tetrahedral intermediate **99**, which undergoes dehydration to the amidine **100**. In the latter, a suitably nucleophilic end group (the anion  $NH^-$ ) adds to the positively charged carbon atom of the nitrile group, thus completing the ring. (For a discussion of the polarization and reaction patterns of a cyano group, see ref. 121.)

One of the two undesired reactions is the formation of an *N*-formyl derivative of the base accompanied by loss of the nitrogen atom that is required for position 3 in the nascent pyrimidine ring.  $\pi$ -Deficiency in the starting material, which disfavors this formylation, encourages dimerization.<sup>122</sup> Thus, 2-aminopyridine-3-carbonitrile (**101**) dimerizes to 2,3'-(2'-amino-pyridyl)-4-aminopyrido[2,3-*d*]pyrimidine (**102**). 2-Aminobenzonitrile does not undergo this reaction, whereas its 5-nitro derivative does so readily. The reaction is the addition of the amino group of one molecule across the cyano group of another to form an intermediate amidine.<sup>122,4</sup>



In spite of these sources of loss, the reaction is useful for both  $\pi$ -excessive and  $\pi$ -deficient nuclei. Thus, formamide has been used successfully to convert 3-amino-4-cyano-2,5-dihydropyrroles (see **11**) to 5,7-dihydropyrrolo[3,4-*d*]pyrimidines (see **13**),<sup>123</sup> 2-amino-3-cyanofurans (see **11**) to furano[2,3-*d*]pyrimidines (see **12**),<sup>120</sup> 4-amino-5-cyanoimidazoles (see **18**) to purines (see **19**),<sup>124</sup> 2-amino-3-cyanopyridines to pyrido[2,3-*d*]pyrimidines (see **3**),<sup>125</sup> and 4-amino-5-cyanopyrimidines (see **2**) to pyrimidino[4,5-*d*]pyrimidines (see **7**).<sup>126,127</sup> Yields ranged from moderate to excellent.

However, some ring systems have posed difficulties. 4-Aminopteridine could not be obtained from 2-amino-3-cyanopyrazine (see **9**), and 2-amino-

<sup>121</sup> A. I. Myers and J. C. Sircar, in "The Chemistry of the Cyano Group" (Z. Rappoport, ed., Chapter 8. Wiley (Interscience), New York, 1970).

<sup>122</sup> E. C. Taylor, A. J. Crovette, and R. J. Knopf, *J. Am. Chem. Soc.* **80**, 427 (1958).

<sup>123</sup> J. F. Cavalla and J. A. D. Willis, *J. Chem. Soc. C*, 693 (1967).

<sup>124</sup> R. N. Prasad and R. K. Robins, *J. Am. Chem. Soc.* **79**, 6401 (1957).

<sup>125</sup> D. M. Mulvey, S. G. Cottis, and H. Tieckelmann, *J. Org. Chem.* **29**, 2903 (1964).

<sup>126</sup> H. Graboyes, G. E. Jaffe, I. J. Pachter, J. P. Rosenbloom, A. J. Villani, J. W. Wilson, and J. Weinstock, *J. Med. Chem.* **11**, 568 (1968).

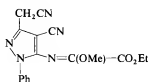
<sup>127</sup> A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

benzonitrile failed to react even with triethyl orthoformate (see Section VI.A,2) but gave a good yield of 4-aminoquinazoline (see 1) with 1,3,5-triazine, which may be regarded as an anhydro trimer of formamide.<sup>128</sup>

Amides other than formamide have been less used but are known to react with *o*-aminonitriles, producing moderate to excellent yields.<sup>129</sup> Most interestingly, *N*-methylformamide converted 5-amino-3,4-dicyano-1-methylpyrazole (see 15) to 1-methyl-3-cyano-4-methylaminopyrrolo[3,4-*d*]pyrimidine (see 16). An obligatory, if unseen, intermediate was the imine 103 which, by a typical Dimroth rearrangement, underwent ring opening and closure to furnish the 4-methylamino group found in the isolated product.<sup>129</sup>



(103)



(104)

We can now review the use of imidates in place of amides. 2-Aminobenzonitrile and methyl *N*-methylacetimidate [MeC(NMe)OMe] were boiled with phosphoric oxide in xylene, giving a moderate yield of 2,3-dimethyl-4-imino-3,4-dihydroquinazoline (see 1 and 103), which underwent the Dimroth rearrangement to the 4-methylamino isomer when warmed with 1 *N* sodium hydroxide.<sup>130</sup> The imide (104), obtained by the action of diazomethane on 3-cyanomethyl-4-cyano-5-ethoxalylamino-1-phenylpyrazole (see 15), gave 4-amino-3-cyanomethyl-6-ethoxycarbonylpyrazolo[3,4-*d*]pyrimidine (see 16) in excellent yield when stirred with cold ethanolic ammonia.<sup>131</sup> Similarly, 3-amino-4-cyanopyrazole, refluxed with benzyl thioacetimidate, gave a good yield of 4-amino-6-methylpyrazolo[3,4-*d*]pyrimidine; other thioimides reacted similarly.<sup>132</sup>

Nitriles can also be substituted for formamide. Benzonitrile and 2-aminobenzonitrile, autoclaved at 200°C, gave a moderate yield of 4-amino-2-phenylquinazoline (see 1). This reaction resembles, and is competitive with, the dimerization of aminonitriles discussed above; it also proceeds by a similar mechanism. Other examples are the condensation of 3-cyanopyridine with 2-amino-3-cyanopyridine to give 2-(3-pyridyl)-4-aminopyrido[2,3-*d*]pyrimidine (see 3) and of 5-cyano-1-methyl-4-aminoimidazole (see 18) with

<sup>128</sup> A. Kreutzberger and M. F. G. Stevens, *J. Chem. Soc. C*, 1282 (1969).

<sup>129</sup> S. M. Hecht and D. Werner, *J. C. S. Perkin I*, 1903 (1973).

<sup>130</sup> D. J. Brown and K. Ienaga, *J. C. S. Perkin I*, 432 (1975).

<sup>131</sup> E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.* **81**, 2456 (1959).

<sup>132</sup> T. H. Dink, A. Kolb, G. Barnathan, and J. Igolen, *J. C. S. Chem. Commun.*, 680 (1973).

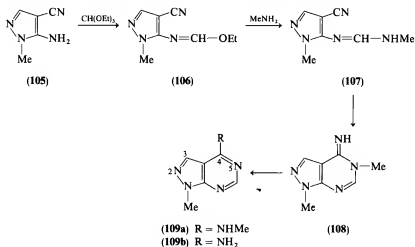


benzonitrile to give 6-amino-7-methylpurine (see **19**), both in good yields.<sup>133</sup> Again, 4-amino-5-cyano-1-methylpyrazole and furonitrile, refluxed with sodium hydroxide in isopropanol for 48 hr, gave an excellent yield of 4-amino-6-(2-furyl)-1-methylpyrazolo[3,4-*d*]pyrimidine (see **16**); several analogs were prepared in this way.<sup>134</sup>

In an unusual reaction, 2-acetamido-3-cyanopyridine, when refluxed with hydroxylamine in toluene for 1 hr, gave a low yield of 4-amino-2-methylpyrido[2,3-*d*]pyrimidine 3-oxide.<sup>135</sup>

## 2. With Ortho Esters Followed by Ammonia or an Amine

It was discovered in 1959 that *o*-aminonitriles could be condensed simultaneously<sup>136</sup> or in turn<sup>131,137</sup> with an ortho ester and ammonia (or a primary amine) to give a 4-amino (or 4-alkylamino) derivative of a fused pyrimidine.



The best yields were obtained when the aminonitrile (such as **105**) was refluxed with a mixture of triethyl orthoformate and acetic anhydride for 2–4 hr, followed by removal of the volatile portion, which left an imidate (such as **106**, 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole). These imidates are fairly stable solids which can be recrystallized from hydro-

<sup>133</sup> E. C. Taylor and A. L. Borrer, *J. Org. Chem.* **26**, 4967 (1961).

<sup>134</sup> H. A. Burch, *J. Med. Chem.* **11**, 79 (1968).

<sup>135</sup> B. Verček, I. Leban, B. Stanovnik, and M. Tišler, *J. Org. Chem.* **44**, 1695 (1979).

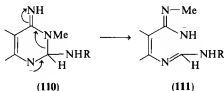
<sup>136</sup> G. Shaw and D. N. Butler, *J. Chem. Soc.*, 4040 (1959).

<sup>137</sup> E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.* **82**, 3147 (1960).

carbons. When set aside at 0°C with ethanolic ammonia or a primary amine, these imidates usually form the 4-imine of the fused pyrimidine (e.g., **108**). However, in rare cases, and the present example is one, the product isolated is an amidine (e.g., **107**), particularly when the reaction with amine has been done in a hydrocarbon.<sup>137</sup> The amidine **107** was stable to boiling ethanol and even to sublimation but could be rapidly isomerized to 1,5-dimethyl-4-iminopyrazolo[3,4-*d*]pyrimidine (**108**) in methanolic sodium methoxide.

The further isomerization of the imine **108** to 1-methyl-4-methylamino-pyrazolo[3,4-*d*]pyrimidine (**109a**) occurred slowly in the presence of methylamine. This change, at least in the 8-azapurine series,<sup>138</sup> can be greatly accelerated by boiling in ethanolic methylamine acetate for 2 hr. When the reagent is not a primary amine but ammonia, no barrier exists to instant prototropy, which gives **109b**.

This Dimroth rearrangement apparently begins with nucleophilic addition of the amine (e.g., MeNH<sub>2</sub>) to the 1,2-C=N group to give **110**, after which the 2,3-bond breaks to form **111**. Rotation is followed by cyclization, in which one molecule of the primary amine is expelled.<sup>139</sup>



Two other examples of the isolation of amidines (of the type **107**) during preparation of amines of the type **109** are 2-aminomethyleneamino-3-cyano-4-methylpyrrole<sup>141</sup> and -thiophene.<sup>143</sup>

Compared to the formamide method, the orthoformate sequence has the advantage of operating at much lower temperatures. It has given good to excellent yields with many  $\pi$ -deficient and  $\pi$ -excessive nuclei. Thus, 3-amino-4-cyano-2,5-dihydropyrroles (see **11**) gave 6,7-dihydropyrrolo[3,4-*d*]pyrimidines (see **13**)<sup>140</sup>; 2-amino-3-cyanopyrroles gave pyrrolo[2,3-*d*]pyrimidines (see **12**)<sup>141</sup>; 2-amino-3-cyanofurans gave furano[2,3-*d*]pyrimidines<sup>142</sup>; 2-amino-3-cyanothiophenes gave thieno[2,3-*d*]pyrimidines, and 2-amino-3-cyanobenzothiophenes reacted similarly<sup>143</sup>; 4-cyano-5-aminoisoxazoles

<sup>138</sup> A. Albert, *J. C. S. Perkin I*, 2659 (1973).

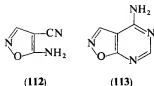
<sup>139</sup> D. J. Brown, in "Mechanisms of Molecular Migration" (B. S. Thyagarajan, ed.), Vol 1, p. 209. Wiley (Interscience), New York, 1968.

<sup>140</sup> T. Sheradsky and P. L. Southwick, *J. Org. Chem.* **30**, 194 (1965).

<sup>141</sup> E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.* **87**, 1995 (1965).

<sup>142</sup> T. I. Temnikova, Y. A. Sharanin, and V. S. Karavan, *Zh. Org. Khim.* **3**, 681 (1967).

<sup>143</sup> E. C. Taylor and J. O. Berger, *J. Org. Chem.* **32**, 2376 (1967).



(112) gave isoxazolo[2,3-*d*]pyrimidines (113)<sup>144</sup>; 3-amino-4-cyanopyrazoles (105) gave pyrazolo[3,4-*d*]pyrimidines (109)<sup>131,137</sup>; 4-amino-5-cyanoimidazoles (see 18) gave purines (see 19)<sup>136,137</sup>; 4-amino-5-cyanopyrimidines (see 2) gave pyrimidino[4,5-*d*]pyrimidines (see 7)<sup>90</sup>; 2-amino-3-cyanopyrazine (see 9) gave pteridines (see 10)<sup>145</sup>; 4-amino-5-cyano-1,2,3-triazoles (see 20) gave 8-azapurines (see 21); and 2-amino-3-cyanopyridine gave 4-aminopyrido[2,3-*d*]pyrimidine (see 3).<sup>135</sup>

To avoid acetylation, no more than one-third as much acetic anhydride as triethyl orthoformate (by volume) should be used. In difficult cases, diethoxymethyl acetate (made by heating triethyl orthoformate with acetic anhydride, then fractionating)<sup>146</sup> has given good results.<sup>147</sup>

Other ortho esters are usually less reactive than orthoformates,<sup>148</sup> but triethyl orthoacetate reacted well with 4-amino-5-cyanoimidazole.<sup>147</sup> 2-Amino-3-cyanopyrazine, after conversion to its 2-amidoxime (—NCHNOH) gave an excellent yield of 4-aminopteridine *N*-oxide with triethyl orthoformate.<sup>149</sup>

### 3. With Amidines

The reaction of amidines with *o*-aminonitriles to give (fused) 4-aminopyrimidines was introduced by Taylor and Ehrhart in 1960.<sup>90</sup> The reaction is thought to proceed through the more complex amidine of type 114, in which R (the methyl group of acetamidine for instance) becomes an alkyl group in the 2-position of the product. At the temperatures used, ring closure is rapid, and no intermediate such as 114 has been isolated.

The amidine is always used as its *acetate* because the hydrochloride gives very little yield. It seems that the acetate is a source of free amidine. Many kinds of amidines are suitable, including *N,N'*-dibutylformamidine, which

<sup>144</sup> E. C. Taylor and E. E. Garcia, *J. Org. Chem.* **29**, 2116 (1964).

<sup>145</sup> A. Albert and K. Ohta, *J. Chem. Soc. C*, 3727 (1971).

<sup>146</sup> H. W. Post and E. R. Erickson, *J. Org. Chem.* **2**, 260 (1937).

<sup>147</sup> R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Am. Chem. Soc.* **90**, 2661 (1968).

<sup>148</sup> R. H. De Wolfe, "Carboxylic Ortho Acid Derivatives," Academic Press, New York, 1970.

<sup>149</sup> M. Kocevar, B. Stanovnik, and M. Tišler, *Heterocycles* **15**, 293 (1981).



(114)



(115)



(116)



(117)

places a butylamino group in the 4-position of the fused pyrimidine after a Dimroth rearrangement too fast for detection.<sup>150</sup>

For most purposes, this amidine synthesis is preferable to the formamide and the ortho ester alternatives; it occurs at a lower temperature than the former, and it is free from the intrusion of intermediates characteristic of the latter. It is particularly useful when an alkyl or chloroalkyl group is required in the 2-position of the product, this pathway being much less explored in the formamide and the ortho ester methods. The amidine reaction is suitable for both  $\pi$ -deficient and  $\pi$ -excessive nuclei.

The original authors favored boiling ethoxyethanol (b.p. 135°C) as solvent, but the reactions stay cleaner longer in simple primary alcohols, a range of which from butanol (b.p. 118°C) to octanol (b.p. 195°C) can supply temperatures suitable for reactions of every degree of difficulty.<sup>150</sup> In most cases butanol suffices. For formamidine acetate, perhaps the most thermolabile of common amidines, boiling *n*-pentanol provides the highest temperature that is compatible with its persistence, and renewed supplies of the amidine should be fed to the reaction mixture at intervals of an hour. The times usual for the reaction are 1–4 hr. Working up usually begins with removal of the solvent in a vacuum.

The following are examples of the use of formamidine (good to excellent yields). 4-Amino-5-cyanopyrimidine (see 2) gave pyrimidino[4,5-*d*]pyrimidines (see 7)<sup>90</sup>; 2-amino-3-cyanopyrrole (see 11) gave pyrrolo[2,3-*d*]pyrimidines (see 12)<sup>141</sup>; 4-amino-5-cyanoimidazole (see 18) gave purines (see 19)<sup>151</sup>; 5-amino-4-cyanooxazole gave 7-aminooxazolo[5,4-*d*]pyrimidine (115)<sup>151</sup>; 2-amino-3-cyanopyrazine (see 9) gave 4-aminopteridine (see 10)<sup>145</sup>; and 4-amino-5-cyano-1,2,3-triazoles, variously alkylated on the ring nitrogen atoms (see 20), gave 8-azapurines (see 21).<sup>150</sup> Note that the amino group in the heterocyclic starting material remains attached; thus, 4-methylamino-1,2,3-triazole-5-carbonitrile (see 20) gave an excellent yield of 6-amino-3-methyl-8-azapurine (116).<sup>64</sup>

Amidines other than formamidine have been used. 4-Amino-5-cyano-1,2,3-triazole and its 1-, 2-, and 3-methyl and 3-benzyl derivatives (see 20) gave

<sup>150</sup> A. Albert, *J. C. S. Perkin I*, 345 (1975).

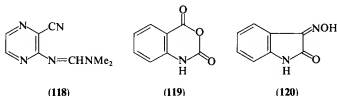
<sup>151</sup> J. P. Ferris and L. E. Orgel, *J. Am. Chem. Soc.* **88**, 3829 (1966).

excellent yields of 6-amino-2-trichloromethyl-8-azapurines (see **21**) with trichloroacetamide acetate in boiling butanol, and good yields of 6-amino-2-methyl- and 6-butylamino-8-azapurines with acetamide acetate and *N,N'*-dibutylformamidine acetate in hexanol and octanol, respectively.<sup>150</sup>

The symmetric dialkylformamidines, made from triethyl orthoformate and a primary amine,<sup>152</sup> are usually easier to make than monoalkylformamidines and (by loss of one molecule of amine during the reaction) serve the same purpose. Attempts to use benzamidine have not been so successful.<sup>126, 153, 154</sup> 5-Cyano-4-hydroxyamino-1-methylimidazole and formamidine gave 6-amino-7-methylpurine 3-oxide (**117**) in excellent yield.<sup>155</sup>

#### 4. With Dimethylformamide and Phosphoryl Chloride Followed by Ammonia or Amines

In 1971, intermediates of type **114** were paralleled by the corresponding tertiary amidines (e.g., **118**), which became the new starting material. These amidines are readily obtained by the action of dimethylformamide and



phosphoryl chloride on the *o*-aminonitriles or (and this often proved to be a great advantage) on the corresponding *o*-aminoamides.<sup>156</sup> A typical product, 3-cyano-2-dimethylaminomethyleneaminopyrazine (**118**) was refluxed with aqueous ammonium acetate for 30 min to give 4-aminopteridine (see **10**) quantitatively. 4-Amino-6-chloropteridine was made similarly without hydrolysis of the labile chlorine substituent. Likewise, methylamine acetate furnished 4-methylaminopteridine in excellent yield.<sup>145</sup> In each case dimethylamine was a by-product.

The 1-, 2-, and 3-methyl and 3-benzyl derivatives of 4-amino-1,2,3-triazole-5-carboxamide (see **20**) were similarly converted (but at 20°C) to 5-cyano-4-dimethylaminomethyleneaminotriazoles (see **21**) in excellent yields. The 1- and 2-methyl examples gave excellent yields of 6-amino-7-

<sup>152</sup> E. C. Taylor and W. A. Ehrhart, *J. Org. Chem.* **28**, 1108 (1963).

<sup>153</sup> E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes, and M. L. Hoeft, *J. Am. Chem. Soc.* **82**, 5711 (1960).

<sup>154</sup> B. R. Baker and J. A. Kozma, *J. Med. Chem.* **11**, 656 (1965).

<sup>155</sup> E. C. Taylor and P. K. Loeffler, *J. Org. Chem.* **24**, 2035 (1959).

<sup>156</sup> J. H. Jones and E. J. Cragoe, *J. Med. Chem.* **11**, 322 (1968).

methyl- and 6-amino-8-methyl-8-azapurines when refluxed with aqueous ammonium acetate (but ammonium chloride was unreactive).<sup>157</sup> The 3-substituted triazoles reacted poorly, even with the acetate. The foregoing 1-and 2-methyl-triazoleamidines gave 7- and 8-methyl-8-azapurine-2-thiones (excellent yields) when refluxed with ethanolic sodium hydrogen sulfide.<sup>157</sup>

Some indirect applications of this reaction have been made. Isatoic anhydride (**119**) was converted to anthranilamide by ammonia in dimethylformamide; addition of phosphoryl chloride converted this amide to 2-dimethylaminomethyleneaminobenzonitrile (analog of **118**), which methylamine converted to 4-methylaminoquinazoline (see **1**). It is remarkable that this was done in one vessel without isolation of intermediates and in good overall yield.<sup>158</sup> Again, isatin-3-oxime (**120**) with phosphoryl chloride and dimethylformamide gave 2-dimethylaminomethyleneaminobenzonitrile, which was cyclized to 4-aminoquinazoline with ammonium acetate and to 4-aminoquinazoline 3-oxide with hydroxylamine, both in excellent yields.<sup>159</sup> Finally, 2-amino-3-cyanopyridine and the dimethylacetal of dimethylformamide, refluxed for 2 hr, gave a good yield of 2-dimethylaminomethyleneamino-3-cyanopyridine, which, when treated with hydroxylamine at 20°C, gave 4-aminopyrido[2,3-*d*]pyrimidine 3-oxide (see **3**) in good yield.<sup>135</sup>

### 5. With Guanidine, Cyanamide, or Cyanoguanidine

It was discovered in 1960 that *o*-aminonitriles react with free guanidine to give annelated 2,4-diaminopyrimidines.<sup>153</sup> Usually, the guanidine is first liberated from a salt (e.g., hydrochloride) by excess ethanolic sodium ethoxide. The sodium chloride is filtered off (excluding carbon dioxide) to complete the liberation of this strong base. The nitrile is then refluxed (1–16 hr) with this ethanolic solution. Alternatively, the nitrile is boiled with guanidine carbonate in ethoxyethanol for 18 hr<sup>124</sup> or fused with guanidine carbonate at 200°C for 1 hr.<sup>126</sup> The latest method is to heat with guanidine acetate in dimethylformamide for 2 hr at 145°C (excellent yields).<sup>160</sup>

For success in this reaction, in which guanidine acetate cannot substitute for the free base, the nitrile group must be attached to a  $\pi$ -deficient nucleus to lend the cyano carbon atom sufficient electropositive character for the

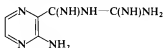
<sup>157</sup> A. Albert, *J. C. S. Perkin I*, 461 (1972).

<sup>158</sup> C. H. Foster and E. V. Elam, *J. Org. Chem.* **41**, 2646 (1976).

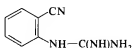
<sup>159</sup> M. N. Deshpande and S. Seshadri, *Indian J. Chem.* **11**, 538 (1973).

<sup>160</sup> E. C. Taylor and T. Kobayashi, *J. Org. Chem.* **38**, 2817 (1973). E. C. Taylor and D. J. Dumas, *J. Org. Chem.* **47**, 116 (1982).

guanidine anion to make a successful nucleophilic attack. The pathway is highlighted by the frequent isolation of intermediates such as **121**, namely, 3-(*N*-amidino)carboxamidines.<sup>156</sup>



(121)



(122)

The following examples produced good to excellent yields. 2-Amino-3-cyanopyrazine (as such or substituted) (see **9**) gave 2,4-diaminopteridines (see **10**)<sup>156,160,161</sup>; 2-amino-3-cyanopyrazine 1-oxide gave pteridine 8-oxides<sup>161</sup>; 4-amino-5-cyanopyrimidine (see **2**) gave 2,4-diaminopyrimidino-[4,5-*d*]pyrimidines (see **7**)<sup>126,153</sup>; 3-amino-4-cyano-2,5-dihydropyrrole (see **11**) gave 2,4-diamino-6,7-dihydropyrrolo[3,4-*d*]pyrimidine (see **13**)<sup>127</sup>; and 4-amino-5-cyano-3-benzyl-1,2,3-triazole (see **20**) gave 1-(4-amino-3-benzyl-1,2,3-triazol-5-yl)-(N-amidino)carboxamidine at 80°C, which closed to 2,6-diamino-9-benzyl-8-azapurine (see **2**) when refluxed in butanol for 1 hr.<sup>150</sup>

In difficult cases, cyanamide or dicyandiamide (cyanoguanidine) has sometimes given better results than guanidine. Thus, 2-aminobenzonitrile and its derivatives, fused with cyanamide and pyridine hydrochloride at 180°C, gave 2,4-diaminoquinazolines in low to moderate yields, and dicyandiamide, fused with hydrochlorides of starting materials at 165°C, was about as good, whereas guanidine, base refluxed 72 hr in 2-ethoxyethanol, was ineffective.<sup>162</sup> Again, cyanamide and 1-cyano-2-aminonaphthalene (also derivatives of this amine), when treated similarly, gave moderate yields of 1,3-diaminobenzo[*f*]quinazolines (**32**).<sup>37</sup> A 2-aminobenzonitrile, heated with dicyandiamide and 10 *N* hydrochloric acid at 160°C, gave a moderate yield of 2,4-diaminoquinazoline.<sup>163</sup>

Annulated 2,4-diaminopyrimidines can also be obtained with chloroformamidine [ $\text{ClC}(\text{NH})\text{NH}_2$ ], which is easily prepared from cyanamide and hydrochloric acid.<sup>164</sup> It was called "cyanamide dihydrochloride" until its true nature was determined.<sup>165</sup> Substituted benzonitriles, heated with chloroformamidine hydrochloride for 30 min in 2-methoxyethyl ether (diglyme) at 150°C, gave good yields of 2,4-diaminoquinazolines; in one

<sup>161</sup> E. C. Taylor, K. L. Perlman, Y.-H. Kim, I. P. Sword, and P. A. Jacobi, *J. Am. Chem. Soc.* **95**, 6413 (1973).

<sup>162</sup> A. Rosowski, J. L. Marini, M. E. Nadel, and E. J. Modest, *J. Med. Chem.* **13**, 882 (1970).

<sup>163</sup> E. F. Elsager, J. Clarke, L. M. Werbel, D. E. Worth, and J. Davoll, *J. Med. Chem.* **15**, 827 (1972).

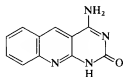
<sup>164</sup> A. Hantzsch and A. Vagt, *Justus Liebigs Ann. Chem.* **314**, 366 (1900).

<sup>165</sup> T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.* **61**, 176 (1939).

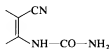
case, an intermediate phenylguanidine (**122**) was isolated.<sup>166</sup> 2-Amino-3-cyanothiophenes (see **11**) gave good to moderate yields of 2,4-diaminothiieno[2,3-*d*]pyrimidines (see **12**).<sup>167</sup>

### 6. With Urea, Isocyanates, or Their Sulfur Analogs

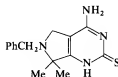
Fusion of an *o*-aminonitrile with urea at 175°–200°C gives an annelated 4-aminopyrimidin-2-one, e.g., the quinolino[2,3-*d*]pyrimidine **123** from 2-amino-3-cyanoquinoline.<sup>117</sup> The reaction is thought to pass through a ureide of the type **124**. Because urea begins to self-condense to the biuret at



(123)



(124)



(125)

about 140°C, the reaction is seldom quite clean, but yields are usually good. Thiourea, more thermally stable, is used in fusion at about 200°C for 10 min to 3 hr<sup>118</sup> or in boiling 2-ethoxyethanol (135°C) for 18 hr<sup>123,168</sup> and usually produces excellent yields of annelated 4-aminopyrimidine-2-thiones.

Additional examples using urea include the following: 2-amino-1-cyanonaphthalene for benzo[*f*]quinazolines (see **32**)<sup>169</sup>; 3-amino-4-cyanopyrazole (see **15**) for pyrazolo[3,4-*d*]pyrimidines (see **16**)<sup>118,170</sup>; a 4-amino-5-cyanimidazole (see **18**) for a purine<sup>171</sup>; and 2-amino-3-cyanothiophene (see **11**) for a thieno[2,3-*d*]pyrimidine (see **12**).<sup>172</sup>

Examples using thiourea include 3-amino-4-cyanopyrazole for pyrazolo[3,4-*d*]pyrimidines<sup>118,168</sup>; 3-amino-4-cyano-1,2,2-trimethyldihydropyrrole (see **11**) for 6,7-dihydropyrrolo[3,4-*d*]pyrimidines (e.g., **125**)<sup>168</sup>; 2-amino-1-cyanonaphthalene for benzo[*f*]quinazolines<sup>169</sup>; and 2-amino-1-cyanocyclopentane for 6,7-dihydrocyclopenta[*d*]pyrimidines.<sup>173</sup> Ammonium

<sup>166</sup> E. F. Elslager, J. Clarke, J. Johnson, L. M. Werbel, and J. Davoll, *J. Heterocycl. Chem.* **9**, 759 (1972).

<sup>167</sup> A. Rosowsky, K. K. N. Chen, and M. Lin, *J. Med. Chem.* **16**, 191 (1973).

<sup>168</sup> J. F. Cavalla, *Tetrahedron Lett.*, 2807 (1964).

<sup>169</sup> A. Rosowsky and E. J. Modest, *J. Org. Chem.* **31**, 2607 (1966).

<sup>170</sup> C. C. Cheng and R. K. Robins, *J. Org. Chem.* **23**, 852 (1958).

<sup>171</sup> E. Shaw, *J. Org. Chem.* **27**, 883 (1962).

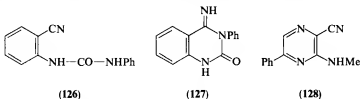
<sup>172</sup> V. D. Patil, D. S. Wise, and L. B. Townsend, *J. C. S. Perkin I*, 1853 (1980).

<sup>173</sup> G. de Stevens, A. Halamandaris, P. Wenk, R. A. Mull, and E. Schlittler, *Arch. Biochem. Biophys.* **83**, 141 (1959).



thiocyanate (at 170°C) has been used in place of thiourea to convert 2-aminobenzonitrile to 4-aminoquinazoline-2-thione (only moderate yield).<sup>174</sup>

The organic isocyanates have proved useful for making 3-alkyl- or 3-aryl-4-iminoquinazolin-2-ones. Thus, phenyl isocyanate and 2-aminobenzonitrile give rise to 2-phenylureidobenzonitrile (**126**) (at 20°C), which



cyclizes to 4-imino-3-phenylquinazolin-2-one (**127**) when heated alone (and faster in boiling ethanolic sodium ethoxide); both reactions are quantitative.<sup>175</sup> However, when 2-aminobenzonitrile was heated with phenyl isocyanate (overnight at 130°C), a Dimroth rearrangement occurred, furnishing a good yield of 4-phenylaminoquinazolin-2-one.<sup>176</sup> 2-Amino-1-cyanonaphthalene and phenyl isocyanate produced a similarly substituted benzo[*f*]quinazoline.<sup>177</sup> 2-Amino-3-cyano-4,5-dihydropyrrole (see **11**) reacted with benzyl, phenyl, and methoxymethyl isocyanates, in two stages, to produce 4-imino-3-*R*-dihydropyrrolo[2,3-*d*]pyrimidines.<sup>178</sup>

Phenyl isothiocyanate behaves similarly. Thus, with 2-aminobenzonitrile it gave *N*-phenylthioureidobenzonitrile in excellent yield (at 50°C, 20 hr, no solvent). This ureide gave a quantitative yield of 4-imino-3-phenylquinazoline-2-thione (analog of **127**) when boiled in methanol for 10 min. Alternatively, when the starting materials were refluxed in benzene for 20 hr, only the cyclized imine was isolated. This, when refluxed with aqueous dimethylformamide (2:1), was rearranged to 4-anilinoquinazoline-2-thione, in excellent yield.<sup>176</sup> 2-Methylaminobenzonitrile and phenyl isothiocyanate in pyridine (2 hr at 100°C) gave an excellent yield of 4-imino-1-methyl-3-phenylquinazoline-2-thione, which rearranged to the 4-phenylamino isomer after 30 hr of refluxing in 0.05 *N* methanolic sodium methoxide.<sup>176</sup> 4-Amino-1- and 4-amino-2-methyl-5-cyano-1,2,3-triazoles (see **20**) and phenyl isothiocyanate, when refluxed for 4 hr in pyridine, gave excellent yields of 6-phenylamino-7-methyl- and 6-phenylamino-8-methyl-8-azapurine-2-thiones (see **21**).<sup>179</sup> The use of methyl isothiocyanate requires a sealed container as

<sup>174</sup> N. K. Ralhan and H. S. Sachdev, *J. Sci. Ind. Res., Sect. B* **19**, 215 (1960).

<sup>175</sup> K. W. Breukink and P. E. Verkade, *Recl. Trav. Chim. Pays-Bas* **79**, 443 (1960).

<sup>176</sup> E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.* **27**, 2622 (1962).

<sup>177</sup> E. C. Taylor, A. McKillop, Y. Shvo, and G. H. Hawks, *Tetrahedron* **23**, 2081 (1967).

<sup>178</sup> H. Wamhoff and B. Welling, *Chem. Ber.* **109**, 2983 (1976).

<sup>179</sup> A. Albert and C. Lin, *J. C. S. Perkin I*, 210 (1977).

in the conversion of 2-aminobenzonitrile to 4-imino-3-methylquinazoline-2-thione.<sup>180</sup>

Finally, 3-amino-2-cyano-5-phenylpyrazine and ethyl chloroformate gave the *N*-ethoxycarbonyl derivative **128**, which cyclized with loss of ammonia to 1-methyl-7-phenylpteridine-2,4-dione in boiling methanolic sodium methoxide (moderate yield).<sup>181</sup>

## B. REACTIONS THAT GIVE PYRIMIDIN-4-ONES OR PYRIMIDINE-4-THIONES

### 1. *With Ortho Esters Followed by Hydrogen Sulfide or with Thioamides (for Pyrimidine-4-thiones)*

The action of sodium hydrogen sulfide on the ethoxymethyleneamino derivatives of nitriles, such as **106**, is useful for preparing annelated pyrimidine-4-thiones.<sup>182</sup> Generally, an *o*-aminonitrile is refluxed with triethyl orthoformate (plus some acetic anhydride except when acetylation is anticipated) for 2 hr or less. The 2-cyano-3-ethoxymethyleneamino intermediate usually<sup>182</sup> is not isolated (but in some cases this is essential<sup>179</sup>). Instead, the volatiles are removed in a vacuum and the residue refluxed with ethanolic 1.5 *N* sodium hydrogen sulfide for 12 hr.

Some examples of this reaction (excellent yields) include the following. 2-Aminobenzonitrile gave quinazoline-4-thione; 1-amino-2-cyanocyclopent-1-ene gave cyclopenteno[*d*]pyrimidine-7-thione; 1-amino-2-cyanocyclohex-1-ene gave cyclohexeno[*d*]pyrimidine-8-thione; 3-amino-4-cyanopyrazole gave pyrazolo[3,4-*d*]pyrimidine-4-thione (see **16**); 4-amino-5-cyanopyrimidine gave pyrimidino[4,5-*d*]pyrimidine-4-thione (see **7**); and 4-amino-3-cyanopiperidine reacted similarly.<sup>182</sup> Moreover, the 1- and 2-methyl and 3-benzyl derivatives of 4-amino-5-cyano-1,2,3-triazole (see **20**) gave the correspondingly alkylated 8-azapurine-6-thiones (see **21**).<sup>179</sup>

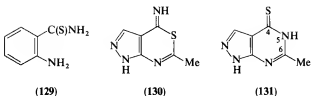
This synthesis has also been carried out in the reverse order by converting 2-aminobenzonitrile to 2-aminothiobenzamide (**129**) by the action of hydrogen sulfide in pyridine containing triethylamine. This thioamide was refluxed with triethyl orthoformate. In one example this reversal was an improvement,<sup>182</sup> but in another it proved to be disadvantageous.<sup>179</sup>

In a related reaction, 2-aminobenzonitrile was heated with phenyl isocyanate in dimethylformamide that had been saturated with dry hydrogen

<sup>180</sup> J. P. Ferris, S. Singh, and T. A. Newton, *J. Org. Chem.*, **44**, 173 (1979).

<sup>181</sup> G. P. Dick, D. Livingston, and H. C. S. Wood, *J. Chem. Soc.*, 3730 (1958).

<sup>182</sup> E. C. Taylor, A. McKillop, and S. Vromen, *Tetrahedron* **23**, 885 (1967).



chloride. This gave an excellent yield of quinazoline-4-thione, but the authors did not rank the method as highly as the previous two. The use of  $^{14}\text{C}$ -labeled dimethylformamide showed that C-2 in the product came from this reagent; the phenyl group was not utilized.<sup>183</sup>

In another synthesis of (fused) pyrimidine-4-thiones, *o*-aminonitriles were condensed with thioacetamide in ethanol that had been saturated with hydrogen chloride. Unstable 1,3-thiazines (such as **130**) could be isolated as intermediates, but a final alkaline treatment gave, for example, 6-methylpyrazolo[3,4-*d*]pyrimidine-4-thione (**131**). When an unsubstituted 2-position was required, thioformanilide in dimethylformamide became the preferred reagent (loss of phenyl group). Yields varied from moderate to good, in favorable cases, but the reaction can be somewhat erratic.<sup>184,185</sup> For another 4-thione-generating reaction, see Section VI.A.4.

## 2. With Carbon Disulfide (for Pyrimidine-2,4-dithiones)

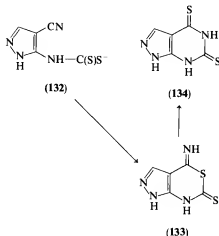
Another example of their many useful reactions for converting *o*-aminonitriles to annelated pyrimidines is the following synthesis by E. C. Taylor and colleagues of annelated pyrimidine-2,4-dithiones.<sup>186</sup> 2-Aminobenzonitrile and carbon disulfide, refluxed in pyridine for 1 hr, gave a quantitative yield of quinazoline-2,4-dithione (see **1**). Four derivatives of 2-aminobenzonitrile behaved similarly, but the reaction failed with 2-amino-5-nitrobenzonitrile because of too little electron availability in the amino group. In less severe cases of electron lack, the authors extended the reflux time to 115 hr with good results. They thought that the first intermediate was the dithiocarbamate anion **132**. The next stage was revealed by the use of 3-amino-4-cyanopyrazole (see **15**) which initially deposited (in excellent yield) 4-iminopyrazolo[4,3-*d*]thiazine-6-thione (**133**); 1*N* sodium hydroxide quickly isomerized the latter compound to pyrazolo[3,4-*d*]pyrimidine-4,6-dithione (**134**). In the same study, 4-amino-5-cyanopyrimidine was converted

<sup>183</sup> E. C. Taylor, S. Vromen, R. V. Ravindranathan, and A. McKillop, *Angew. Chem., Int. Ed. Engl.* **5**, 308 (1966).

<sup>184</sup> E. C. Taylor and J. A. Zoltewicz, *J. Am. Chem. Soc.* **83**, 248 (1961).

<sup>185</sup> J. A. Zoltewicz and T. W. Sharpless, *J. Org. Chem.* **32**, 2681 (1967).

<sup>186</sup> E. C. Taylor, A. McKillop, and R. N. Warrenner, *Tetrahedron* **23**, 891 (1967).



to pyrimidino[4,5-*d*]pyrimidine-2,4-dithione (see 7)<sup>186</sup>; in addition, a glycoside of 4-amino-5-cyanoimidazole (see 18) gave the corresponding purine-2,6-dithione (see 19).<sup>187</sup> Similarly, 1- and 2-methyl-4-amino-5-cyano-1,2,3-triazoles (see 20) produced 7- and 8-methyl-8-azapurine-2,6-dithiones (see 21) quantitatively.<sup>179</sup>

An ingenious solution to the problem of slowly reacting (weakly basic) *o*-aminonitriles was to replace the carbon disulfide by potassium *O*-ethyl dithiocarbonate ("xanthogenate") (EtO—CS<sub>2</sub>K),<sup>188</sup> which slowly liberates carbon disulfide above 110°C. Thus, 2-amino-5-nitrobenzonitrile gave an excellent yield of 6-nitroquinazoline-2,4-dithione when boiled with this salt in butanol for 4 hr.<sup>189</sup> Excellent yields of 8-azapurine-2,6-dithione and its 9-methyl and 9-benzyl derivatives were similarly obtained.<sup>179</sup> For more reluctant reactions, boiling dimethylformamide proved to be a useful solvent.<sup>189</sup>

Excellent yields of annelated 4-thioxypyrimidin-2-ones have been obtained by condensing *o*-aminonitriles with carbonyl sulfide (24 hr in boiling ethanolic sodium ethoxide). Thus, 2-amino-3-cyanothiophene (see 11) gave 4-thioxothieno[2,3-*d*]pyrimidin-2-one (135), and 3-amino-4-cyanopyrazole (see 15) formed 4-thioxopyrazolo[3,4-*d*]pyrimidin-6-one (see 16). The reaction is thought to follow the course of the above carbon disulfide reaction.<sup>190</sup>

<sup>187</sup> R. J. Rousseau and L. B. Townsend, *J. Org. Chem.* **33**, 2828 (1968).

<sup>188</sup> C. C. Price and G. W. Stacy, *Org. Synth., Collect. Vol.* **3**, 668 (1955).

<sup>189</sup> H.-J. Kabbe, *Synthesis*, 268 (1972).

<sup>190</sup> M. A. Hernández, F.-L. Chung, R. A. Earl, and L. B. Townsend, *J. Org. Chem.* **44**, 3941 (1981).



(135)

### 3. With Acylating Agents Followed by Acids, Bases, or Hydrogen Peroxide (for Pyrimidin-4-ones)

Many *o*-acylaminobenzonitriles have been cyclized by acid or alkali. For example, 2-(*N*-formyl)methylaminobenzonitrile gave a moderate yield of 1-methylquinazolin-4-one (see **1**) when boiled with 2*N* hydrochloric acid or 1*N* sodium hydroxide for 2 hr, although these may seem to be hydrolytic conditions.<sup>191</sup> 2-(*N*-Acetyl)methylaminobenzonitrile gave a better yield of 1,2-dimethylquinazolin-4-one when set aside at 20°C in ethanolic hydrogen chloride.<sup>192</sup>

However, 70 hr at 200°C was necessary to convert 2-aminobenzonitrile in formic acid to quinazolin-4-one.<sup>193</sup> Acetic anhydride formed the 2-methyl homolog under similar conditions, but higher anhydrides reacted very little.<sup>194</sup>

This type of reaction acquired more significance when Bogert and Hand changes to alkaline hydrogen peroxide.<sup>194</sup> Although 2-formamidobenzonitrile was spoiled by the new conditions (5% aqueous sodium peroxide at 60°C for two hr), the 2-acetamido and higher acyl derivatives gave quantitative yields of 2-alkylquinazolin-4-ones.<sup>195</sup> The reaction mechanism probably depends on the formation and ring closure of the amide.<sup>196</sup> The few applications of the Bogert-Hand reaction to heterocyclic nuclei revolve mainly around conversion to pyrazolo[3,4-*d*]pyrimidin-4-ones of 5-amino-4-cyanopyrazoles (see **15**) in good yields.<sup>134,196</sup>

Special starting materials or conditions have been used to introduce unusual substituents (without using hydrogen peroxide). Thus, 2-oxalylaminobenzonitrile and cold dilute hydrochloric acid gave 4-oxoquinazoline-2-carboxylic acid (**136**) (no yield given).<sup>197</sup> The urethane, 2-methoxycar-

<sup>191</sup> D. J. Fry, J. D. Kendall, and A. J. Morgan, *J. Chem. Soc.* 5062 (1966).

<sup>192</sup> E. C. Taylor and Y. Shvo, *J. Org. Chem.* **33**, 1719 (1968).

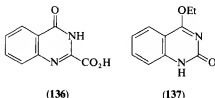
<sup>193</sup> M. T. Bogert and W. F. Hand, *J. Am. Chem. Soc.* **25**, 935 (1903).

<sup>194</sup> M. T. Bogert and W. F. Hand, *J. Am. Chem. Soc.* **24**, 1031 (1902).

<sup>195</sup> M. T. Bogert and W. F. Hand, *J. Am. Chem. Soc.* **28**, 94 (1906).

<sup>196</sup> C. C. Cheng and R. K. Robins, *J. Org. Chem.* **23**, 191 (1958).

<sup>197</sup> A. Reissert and F. Grabe, *Ber. Dtsch. Chem. Ges.* **42**, 3710 (1909).



bonylaminobenzonitrile, gave 4-ethoxyquinazolin-2-one (137) in boiling ethanolic sodium ethoxide,<sup>175</sup> and the same reagent converted 2-formamido-benzonitrile to 4-ethoxyquinazoline (homologs behaved similarly) in good yield.<sup>198</sup>

## VII. From Rings with an Amino Group Adjacent to an Amide or Thioamide Group

### A. FROM AMIDES (FOR PYRIMIDIN-4-ONES)

#### 1. With Formic Acid

This reaction was originally performed in 1885 when Weddige condensed 2-aminobenzamide with formic acid to give 2-formamidobenzamide, which when maintained in the melted state "for some time" became dehydrated to quinazolin-4-one (see 1). No details or yield were given for either reaction,<sup>199</sup> but Knappe reported that 2-formamidobenzamide required 2–3 hr for ring closure at 170°C. He added that 2-formamido(*N*-methyl)benzamide required "many hours" at 195°C, and the isomeric 2-(*N*-methylformamido)benzamide gave only a poor yield after a long period of heating.<sup>200</sup> These results gave early warning of the barrier to ring closure imposed by a secondary amino group. This problem, which becomes acute in highly  $\pi$ -deficient nuclei, can be overcome, if the  $\pi$ -deficiency is mild, by boiling the amide with a mixture of formic acid and acetic anhydride.

Thus, 4-amino-1-methylimidazole-5-carboxamide (see 18) gave a good yield of 9-methylpurin-6-one (see 19) when refluxed with these reagents for 2 hr,<sup>201</sup> and 4-aminoimidazole-5-carboxamide required only 30 min at 70°C.<sup>202</sup> In the more  $\pi$ -deficient pyrazine series, 2 hr of boiling with the

<sup>198</sup> K. W. Breukink, L. H. Krol, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas* **76**, 401 (1957).

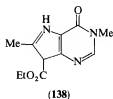
<sup>199</sup> A. Weddige, *J. Prakt. Chem.* [2] **31**, 124 (1885).

<sup>200</sup> E. Knappe, *J. Prakt. Chem.* [2] **43**, 209 (1891).

<sup>201</sup> A. H. Cook and E. Smith, *J. Chem. Soc.*, 2329 (1949).

<sup>202</sup> E. Shaw, *J. Biol. Chem.* **185**, 439 (1950).

same reagents converted 2-aminopyrazine-3-(*N*-methyl)carboxamide (see 9) to 3-methylpteridin-4-one (see 10),<sup>203</sup> and 2-methylaminopyrazine-3-carboxamide to 1-methylpteridin-4-one, in good yield.<sup>204</sup> The relative ease of closure of  $\pi$ -excessive examples is illustrated by 3-amino-4-ethoxycarbonyl-5-methyl-2-methylaminocarbonylpyrrole (see 11), which gave an excellent yield of 7-ethoxycarbonyl-3,6-dimethylpyrrolo[3,2-*d*]pyrimidin-4-one (138) when simply refluxed with formic acid for 3 hr.<sup>205</sup>



Alkaline closures are also possible. 2-Formamido-6-methylpyrazine-3-(*N*-methyl)carboxamide gave a good yield of 3,7-dimethylpteridin-4-one when boiled in 0.5 *N* sodium bicarbonate for 5 min.<sup>206</sup> For the less  $\pi$ -deficient 4-formamidoimidazole-5-carboxamide, 0.05 *N* sodium bicarbonate sufficed to produce an excellent yield of hypoxanthine (purin-6-one).<sup>204</sup> These alkaline conditions are well tolerated by glycosides.

When more powerful cyclizing reagents are required, the use of formamide and particularly ortho esters, especially when acid-catalyzed, can be recommended (see Sections 3 and 4 below).

## 2. With Other Acids or with Esters, Acid Chlorides, or Acid Anhydrides

2-Benzamidobenzamide was converted to 2-phenylquinazolin-4-one by heating at 250°C for 1 hr (no yield given).<sup>207</sup> Difficulty in closing the ring was experienced when one or both of the amino groups were secondary.<sup>208</sup>

Alkaline closures proceed more readily.<sup>207</sup> 2-Benzamidobenzamide and several of its derivatives gave 2-phenyl- and substituted phenylquinazolin-4-ones when heated with 1.3 *N* sodium hydroxide for 15 min (good

<sup>203</sup> A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.* 4219 (1952).

<sup>204</sup> A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956).

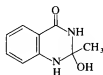
<sup>205</sup> T. Murata, T. Sugawara, and K. Ukawa, *Chem. Pharm. Bull.* **26**, 3080 (1978).

<sup>206</sup> W. Curran and R. Angier, *J. Org. Chem.* **26**, 2364 (1961).

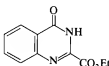
<sup>207</sup> M. Körner, *J. Prakt. Chem.* [2] **36**, 155 (1887).

<sup>208</sup> A. Weddige, *J. Prakt. Chem.* [2] **36**, 141 (1887).

to quantitative yields).<sup>209</sup> Some light is shed on the course of the reaction by 2-acetamidobenzamide, which, when warmed briefly with aqueous sodium bicarbonate, deposited 2-hydroxy-2-methyl-1,2-dihydroquinazolin-4-one (**139**); this compound changed to 2-methylquinazolin-4-one when heated to 210°C.<sup>210</sup>

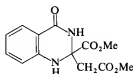


(139)



(140)

Turning to esters, diethyl oxalate condensed with 2-aminobenzamide to give ethyl 4-oxoquinazoline-2-carboxylate (**140**) when set aside in ethanolic sodium ethoxide at 25°C for 2 days (quantitative). Similarly, but at 75°C, 2-aminopyridine-3-carboxamide furnished ethyl 4-oxopyrido[2,3-*d*]pyrimidine-2-carboxylate (see **3**), and 2-aminoquinoline-3-carboxamide produced ethyl 4-oxoquinolino[2,3-*d*]pyrimidine-2-carboxylate (see **123**).<sup>211</sup> 2-Aminobenzamide and dimethyl acetylenedicarboxylate, in refluxing methanol, gave 2-methoxycarbonyl-2-methoxycarbonylmethyl-1,2-dihydroquinazolin-4-one (**141**) in excellent yield through dimethyl (2-carboxamidoanilino)formate.<sup>212</sup>



(141)

Acid chlorides and anhydrides are valued for their capacity to attack the more  $\pi$ -deficient of the *o*-aminoamides, which acylate only with difficulty; yet the acylated products cyclize immediately when placed in cold 1*N* potassium hydroxide. For example, 2-acetamido- and 2-benzamidopyrazine-3-carboxamide (see **9**), when treated in this way, give 2-methyl- and 2-phenylpteridin-4-one (see **10**) in excellent yields.<sup>213</sup> However, the synthesis

<sup>209</sup> H. Stephen and G. Wadge, *J. Chem. Soc.*, 4420 (1956).

<sup>210</sup> L. Errede, M. Etter, R. Williams, and S. Darnauer, *J. C. S. Perkin I*, 233 (1980).

<sup>211</sup> S. Nakanishi and S. S. Massett, *Org. Prep. Proced. Int.* **12**, 219 (1980).

<sup>212</sup> T. F. Lemke, H. W. Snady, and N. D. Heindel, *J. Org. Chem.* **37**, 2337 (1972).

<sup>213</sup> A. Albert, *J. C. S. Perkin I*, 1574 (1979).

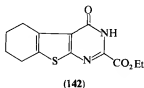


of these starting materials from 2-aminopyrazine-3-carboxamide required acetic anhydride at 100°C for 10 hr and benzoyl chloride in pyridine (bath at 130°C) for 12 hr.

Acyating agents derived from stronger acids catalysed ring closure in this series. Thus, attempted acylation of 2-aminopyrazine-3-carboxamide with formic acid or trifluoroacetic anhydride gave very little of the acyl derivative but much of the pteridin-4-one, even while much starting material remained unattacked.<sup>213</sup> In such cases it proved best to use forcing conditions in order to complete both stages in one step. Hence, heating the amide with formic acid and acetic anhydride at 120°C gave pteridin-4-one, and heating the amide with trifluoroacetic anhydride (36 hr at 110°C) furnished 2-trifluoromethylpteridin-4-one, both in excellent yields.<sup>213</sup>

In the absence of  $\pi$ -deficiency, conditions are milder. 2-Acetamidobenzoic acid and sodium acetate, refluxed for 1 hr in acetic anhydride, gave an excellent yield of 2-methyl-3-phenylquinazolin-4-one.<sup>214</sup>

Ethoxalyl chloride ( $\text{EtO}_2\text{C}-\text{COCl}$ ) in pyridine converted 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide to the 2-ethoxalylamino analog, which was heated at 260°C to give ethyl 5,6,7,8-tetrahydro-4-oxobenzo-thieno[2,3-*d*]pyrimidine-2-carboxylate (**142**) (moderate yield).<sup>215</sup>



2-Benzamidobenzanilide, which resisted ring closure by boiling acetic anhydride, was changed to 2,3-diphenylquinazolin-4-one in boiling benzoyl chloride (5 min; excellent yield).<sup>214</sup>

### 3. With Formamide or Other Amides

The first use of formamide to convert an *o*-aminoamide to an annelated pyrimidin-4-one seems to have been Price and Curtin's synthesis of pyrido[3,2-*d*]pyrimidin-4-one (see **6**) from 3-aminopyridine-2-carboxamide.<sup>216</sup> This reaction has been used mainly on  $\pi$ -deficient starting materials for which it is more efficient than formic acid and, on occasion, triethyl

<sup>214</sup> P. A. Petyunin and Yu. V. Kozhevnikov, *Zh. Obshch. Khim.* **30**, 2352 (1960) [*CA* **55**, 9402 (1961)].

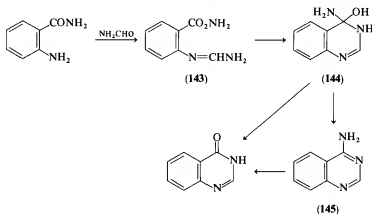
<sup>215</sup> D. Temple, J. Yevich, R. Covington, C. Hanning, R. Seidehand, H. Mackey, and M. Bartek, *J. Med. Chem.* **22**, 505 (1979).

<sup>216</sup> C. C. Price and D. Y. Curtin, *J. Am. Chem. Soc.* **68**, 914 (1946).

orthoformate.<sup>217</sup> Two parts, by volume, of formamide usually suffice, and yields are generally excellent.

The ideal bath temperature is often between 180° and 220°C; it should be determined in preliminary experiments spaced at intervals of 10°C. Below the optimal temperature, much starting material remains, but above it severe charring often occurs. The uncontrolled variables introduced by "boiling" formamide were discussed in Section VI,A,1. The most productive time for the reaction has been about 45 min in many cases. The working up is accomplished by cooling, then adding water or preferably an organic solvent such as acetone, and then filtering off the product after refrigeration. Alternatively, the formamide can be distilled off at 160°C/25 mm Hg or 145°C/7 mm Hg.

It has been suggested that the first step is formylation of the ring-attached amino group.<sup>218</sup> Scheme 1 shows a more likely course, in which the initial



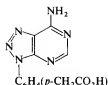
SCHEME 1

attack on 2-aminobenzamide furnishes the amidine **143** via the usual tetrahedral intermediate. It is expected that the primary amino group of this amidine adds across the C=O bond of the carboxamide group to give the tetrahedral intermediate **144**. Loss of ammonia would then give the usual pyrimidin-4-one type of product. However, it has been shown recently that a 4-aminopyrimidine product (**145**) can be isolated if the starting material is a carboxylic acid. For example, 4-amino-3-(*p*-carboxymethylphenyl)-1,2,3-triazole-5-carboxamide (see **20**), when heated with formamide (1 hr at 200°C), gave an excellent yield of 6-amino-9-(*p*-carboxymethylphenyl)-8-azapurine (**146**).<sup>219</sup>

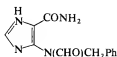
<sup>217</sup> A. Dornow and J. Helberg, *Chem. Ber.* **93**, 2001 (1960).

<sup>218</sup> N. J. Leonard and W. V. Ruyle, *J. Org. Chem.* **13**, 903 (1948).

<sup>219</sup> A. da Settimo, O. Livi, P. Ferrarini, and G. Primofiore, *Farmaco, Ed. Sci.* **35**, 279 (1980).



(146)



(147)

The formamide reaction has been successfully used to convert a 2-aminopyridine-3-carboxamide to pyrido[2,3-*d*]pyrimidin-4-ones (see **3**)<sup>220</sup>; 3-aminopyrazole-4-carboxamide (see **15**) to pyrazolo[3,4-*d*]pyrimidin-4-ones (see **16**)<sup>118</sup>; 4-aminopyrazole-3-carboxamide to pyrazolo[4,3-*d*]pyrimidin-7-ones (see **17**)<sup>221</sup>; many 4-amino-1,2,3-triazole-5-carboxamides (see **20**) to 8-azapurin-6-ones (see **21**)<sup>157,217,222-226</sup>; and 4-aminoimidazole-5-carboxamides (see **18**) to purin-6-ones (see **19**).<sup>124,202,227,228</sup>

Secondary amines are suitable starting materials, as in the conversion of 4-amino-1,2,3-triazole-5-(*N*-methyl)carboxamide and its 3-benzyl<sup>63</sup> and 3-methyl<sup>226</sup> homologs to the corresponding 8-azapurin-6-ones (see **21**) and of 2-aminobenz(*N*-butyl)amide to 3-butylquinazolin-4-one.<sup>218</sup> Surprisingly, 2-amino-5,6-diphenylpyrazine-3-(*N*-benzyl)carboxamide lost the benzyl group in producing 6,7-diphenylpteridin-4-one in good yield.<sup>229</sup> Secondary amines, such as 2-methylaminobenzamide<sup>218</sup> and 4-(*N*-formyl)benzylaminoimidazole-5-carboxamide (**147**)<sup>227</sup> tend to give lower yields. 4-Methylamino-1,2,3-triazole-5-carboxamide and its 3-benzyl derivative (see **20**) performed much better in acidified triethyl orthoformate.<sup>64</sup>

Dimethylformamide diethylacetal converted 2-benzylaminopyrazine-3-carboxamide to 1-benzylpteridin-4-one (see **10**) in good yield after 1 hr of refluxing, although this pyrazine had resisted the more common cyclizing agents.<sup>230</sup>

Except for trifluoroacetamide, which gave an excellent yield of 2-trifluoromethylpurin-6-one (see **19**) when refluxed for 2 hr with 4-aminoimidazole-5-carboxamide,<sup>231</sup> the higher amides lack the reactivity of formamide.

<sup>220</sup> S. G. Cottis and H. Tieckelmann, *J. Org. Chem.* **26**, 79 (1961).

<sup>221</sup> R. K. Robins, F. W. Furcht, A. D. Grauer, and J. W. Jones, *J. Am. Chem. Soc.* **78**, 2418 (1956).

<sup>222</sup> A. Albert and K. Tratt, *J. Chem. Soc. C*, 344 (1968).

<sup>223</sup> A. Albert, *J. Chem. Soc. C*, 2076 (1968).

<sup>224</sup> A. Albert, *J. Chem. Soc. C*, 152 (1969).

<sup>225</sup> A. Albert, *J. Chem. Soc. C*, 2379 (1969).

<sup>226</sup> A. Albert and D. Thacker, *J. C. S. Perkin I*, 468 (1972).

<sup>227</sup> E. Shaw, *J. Am. Chem. Soc.* **80**, 3899 (1958).

<sup>228</sup> E. Shaw, *J. Org. Chem.* **30**, 3371 (1965).

<sup>229</sup> E. C. Taylor, J. A. Carbon, and D. R. Hoff, *J. Am. Chem. Soc.* **75**, 1904 (1953).

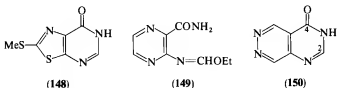
<sup>230</sup> W. F. Kier, A. H. MacLennan, and H. C. S. Wood, *J. C. S. Perkin I*, 1321 (1977).

<sup>231</sup> A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.* **80**, 5744 (1958).

However, it was recently discovered that they are activated by alkoxides. For example, benzamide and 2-aminopyrazine-3-carboxamide, in boiling butanolic sodium butoxide, gave an excellent yield of 2-phenylpteridin-4-one (see 10).<sup>213</sup>

#### 4. With Ortho Esters

Triethyl orthoformate was introduced by Cook and Smith in 1949 to cyclize 5-amino-2-methylthiothiazole-4-carboxamide to 6-methylthio[5,4-*d*]pyrimidin-4-one (148) in excellent yield.<sup>201</sup> Usually, the starting material is vigorously refluxed with equal volumes of this reagent and acetic anhydride for 2 hr in a bath at 150°C. In some cases, when the acetic anhydride was omitted, ethoxymethyleneamino derivatives, such as 149, accumulated, thus



displaying the course of the reaction.<sup>232</sup>

Other successful uses of triethyl orthoformate include formation of pteridin-4-ones from 2-aminopyrazine-3-carboxamide (see 9) and its derivatives<sup>127,229,233,234</sup>; *cis*- and *trans*-4a,5,6,7,8,8a-hexahydroquinazolin-4-ones from the related 2-aminocyclohexanecarboxamides<sup>61,65</sup>; pyrido[2,3-*d*]pyrimidin-4-ones (see 3) from 2-aminopyridine-3-carboxamide<sup>235</sup>; thiazolo[5,4-*d*]pyrimidin-4-one (see 148) from 5-aminothiazole-4-carboxamide<sup>236</sup>; and purin-6-ones (see 19) from 4-aminoimidazole-5-carboxamide.<sup>232,237</sup> Any partial acetylation of  $\pi$ -excessive products can be reversed by a final alkaline treatment.<sup>238</sup>

Dimethylformamide has been used in place of acetic anhydride, as when 2-methyl-4-aminoimidazole-5-carboxamide hydrochloride was quantitatively converted to 8-methylpurin-6-one after only 5 min of boiling.<sup>239</sup> Treated similarly, 4-aminopyridazine-5-carboxamide gave an excellent yield of

<sup>232</sup> C. L. Leese and G. M. Timmis, *J. Chem. Soc.*, 3818 (1961).

<sup>233</sup> W. V. Curran and R. B. Angier, *J. Am. Chem. Soc.* **26**, 2364 (1961).

<sup>234</sup> J. H. Jones, J. B. Bicking, and E. J. Cragoe, *J. Med. Chem.* **10**, 899 (1967).

<sup>235</sup> A. Dornow and D. Wille, *Chem. Ber.* **98**, 1505 (1965).

<sup>236</sup> M. Sekiya and Y. Osaki, *Chem. Pharm. Bull.* **13**, 1319 (1965).

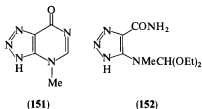
<sup>237</sup> R. G. Glushkov and O. Yu. Maghidson, *Zh. Obshch. Khim.* **31**, 1173, 1906 (1961) [*CA* **55**, 23547, 27354 (1961)].

<sup>238</sup> J. A. Montgomery, *J. Am. Chem. Soc.* **78**, 1928 (1956).

<sup>239</sup> E. Richter, P. K. Loeffler, and E. C. Taylor, *J. Am. Chem. Soc.* **82**, 3144 (1960).

pyrimidino[4,5-*d*]pyridazin-4-one (150).<sup>240</sup> Ethyl orthoformate has also been used to make *N*-hydroxy heterocycles from *o*-amino-*N*-hydroxyaminocarbonyl types of starting material (see Section IX).<sup>241,242</sup>

Secondary amines, debarred from the normal pathway, which requires primary amines, can present difficulties. 1-Methyl-5-methylaminoimidazole-5-carboxamide gave 3,9-dimethylpurin-6-one only after the triethyl orthoformate had *first* been refluxed with acetic anhydride to build up diethoxymethyl acetate in the reagent.<sup>243</sup> Many unsuccessful attempts were made to cyclize 4-methylamino-1,2,3-triazole-4-carboxamide and its 3-benzyl derivative (see 20); these attempts usually led to migration (Dimroth) of the methyl group from the exocyclic nitrogen atom to N-3 (displacing the benzyl group when present). However, excellent yields of the desired 3-methyl-8-azapurin-6-one (151) and its 9-benzyl derivative were obtained by stirring the triazole with a mixture of 10 *N* hydrochloric acid and triethyl orthoformate for 1 hr at 100°C or 24 hr at 25°C.<sup>64</sup> The mechanism of this surprising reaction is thought to be an electrophilic attack by the diethoxycarbenium ion  $[\text{HC}^+(\text{OEt})_2]$  to give the acetal 152, which loses two molecules of ethanol to furnish the isolated products.<sup>64</sup>



Some successful syntheses have also been effected with triethyl orthoacetate and acetic anhydride leading to 2-methyl-<sup>213</sup> and 2,6-dimethylpteridin-4-one<sup>244</sup> from the relevant pyrazine, as well as to 2-methyl-6-cyano-7-methoxy-pyrido[2,3-*d*]pyrimidin-4-one (see 3) from the corresponding pyridine.<sup>245</sup>

### 5. With Amidines or Guanidine

Amidines were first condensed with *o*-aminoamides in 1965 when Baker and Kozma fused benzamide, 4-aminopyrazole-5-carboxamide, and sodium

<sup>240</sup> T. Kinoshito and R. N. Castle, *J. Heterocycl. Chem.* **5**, 845 (1968).

<sup>241</sup> E. C. Taylor, C. C. Cheng, and O. Vogel, *J. Org. Chem.* **24**, 2019 (1959).

<sup>242</sup> E. C. Taylor, K. L. Perlman, I. P. Sword, M. Sequin-Frey, and P. A. Jacobi, *J. Am. Chem. Soc.* **95**, 6407 (1973).

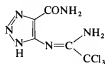
<sup>243</sup> T. Itaya and K. Ogawa, *Heterocycles* **6**, 965 (1977).

<sup>244</sup> J. Clark and G. Neath, *J. Chem. Soc. C*, 1112 (1966).

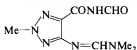
<sup>245</sup> D. M. Mulvey, S. G. Cottis, and H. Tieckelman, *J. Org. Chem.* **29**, 2903 (1964).

acetate at 200°C, obtaining good yields of pyrazolo[4,3-*d*]pyrimidin-7-one and derivatives (see 17).<sup>246</sup> This type of reaction is much more manageable in boiling primary alcohols.<sup>213</sup> Butanol usually suffices, but boiling octanol (200°C) is often required for acetamidine.<sup>247</sup> In this way, 4-amino-1,2,3-triazole-5-carboxamide and its 1- and 2-methyl derivatives were condensed with the acetates of formamidine, acetamidine, trichloroacetamidine,<sup>248</sup> and benzamidine to give the correspondingly 2-substituted 8-azapurin-6-ones (see 21). Yields were generally excellent but were depressed by a 3-alkyl group in the triazole.<sup>213</sup>

The corresponding hydrochlorides do not react, so that the acetates seem to form a steady source of the more volatile and thermolabile bases. The course of the reaction is revealed by trichloroacetamidine, which takes the triazole no farther than an ethylideneamino derivative (153). This can be cyclized rapidly in cold 0.5 *N* potassium hydroxide to 2-trifluoromethyl-8-azapurin-6-one.<sup>248</sup> Formamidine acetate has also been used to convert 2-aminopyrazine-3-carboxamide to pteridin-4-one in good yield.<sup>213</sup>



(153)



(154)

A little explored reaction begins with 4-dimethylaminomethyleneamino-2-methyl-1,2,3-triazole-5-(*N*-formyl)carboxamide (154) and its 1-methyl isomer. These can be prepared in good yield by stirring the *o*-aminoamide with dimethylformamide at 20°C, as in preparing the corresponding nitriles (Section VI.A.4), but avoiding excess of phosphoryl chloride.<sup>157</sup> (They are often isolated as by-products in preparing the nitriles.) When heated at its melting point, the amidineamide 154 immediately cyclizes (quantitatively) to 8-methyl-8-azapurin-6-one. The primary amide corresponding to 154, which rapidly and quantitatively precipitates out when the acidic 154 is dissolved in 1 *N* sodium hydroxide, can also be obtained by oxidizing the corresponding nitrile (100) with hydrogen peroxide. It, too, cyclizes to 8-methyl-8-azapurin-6-one when heated just above its melting point.<sup>157</sup>

3-Aminopyridine-2-carboxamide, when fused with guanidine carbonate at 170°C, gave a moderate yield of 2-aminopyrido[3,2-*d*]pyrimidin-4-one (see 6).<sup>249</sup>

<sup>246</sup> B. R. Baker and J. A. Kozma, *J. Med. Chem.* **11**, 656 (1965).

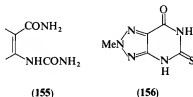
<sup>247</sup> A. Albert and A. M. Trotter, *J. C. S. Perkin I*, 922 (1979).

<sup>248</sup> A. Albert and B. Paal, *Chem. Ind. (London)*, 874 (1974).

<sup>249</sup> F. Korte, *Chem. Ber.* **85**, 1012 (1952).

6. *With Urea, Isocyanates, or Phosgene (or Their Sulfur Analogs) or with Ethyl Chloroformate, Diethyl Carbonate, or Carbon Disulfide*

Fusion of *o*-aminoamides with urea to give annelated pyrimidine-2,4-diones was introduced by Abt in 1889.<sup>250</sup> Usually, the starting material and an equal weight (sometimes more) of urea are heated at 175°C for 2 hr, but other conditions (from 160° to 200°C and from 20 min to 5 hr) have been advocated in special cases. Yields have varied from good to excellent. At lower temperatures, ureide intermediates of the type **155** have been isolated, indicating the course of the reaction.



Urea has been used successfully to convert 4-aminoimidazole-5-carboxamide (and its derivatives) to purine-2,6-diones (see **19**)<sup>124,202</sup>; 2-amino-,<sup>250,251</sup> 2-methylamino-,<sup>252</sup> and 2-anilinobenzamides<sup>253</sup> to quinazoline-2,4-diones (see **1**); 3-aminopyrazolo-4-carboxamide<sup>118</sup> and 4-aminopyrazole-3-carboxamide<sup>221</sup> to the related pyrazolopyrimidinediones (see **16** and **17**); and 4-amino-1- and 4-amino-2-methyl-1,2,3-triazole-5-carboxamides to 8-azapurine-2,6-diones (see **21**).<sup>254</sup>

Thiourea has been used similarly to prepare, at 175°C (3 hr) up to 205°C (20 min), good yields of annelated 2-thioxopyrimidin-4-ones such as 8-methyl-2-thioxo-8-azapurin-6-one (**156**) from 4-amino-1,2,3-triazole-5-carboxamides (see **20**),<sup>254</sup> as well as pyrazolo[4,3-*d*]- and pyrazolo[3,4-*d*]pyrimidinediones from the appropriate aminopyrazolecarboxamides (see **15**)<sup>124,221</sup> and thieno[2,3-*d*]pyrimidine-2,4-diones (see **12**) from 2-aminothiophene-3-carboxamide.<sup>255</sup>

A reagent related to urea, namely, *N*-acetylated *N,N'*-diisopropylcarbodiimide, gave an excellent yield of 3-isopropyl-2-isopropylaminoquinazolin-

<sup>250</sup> W. Abt, *J. Prakt. Chem.* [2] **39**, 141 (1889).

<sup>251</sup> F. E. Sheibley, *J. Org. Chem.* **3**, 414 (1938).

<sup>252</sup> M. Vincent, J. Maillard, and M. Bénard, *Bull. Soc. Chim. Fr.*, 119 (1963).

<sup>253</sup> S. Toyoshima, K. Shimada, S. Hamano, and T. Ogo, *Yakugaku Zasshi* **85**, 502 (1965) [*CA* **63**, 7009 (1965)].

<sup>254</sup> A. Albert and H. Taguchi, *J. C. S. Perkin I*, 449 (1972).

<sup>255</sup> F. Sauter and W. Deinhammer, *Monatsh. Chem.* **104**, 1593 (1973).

4-one when refluxed with 2-aminobenzamide in ethanolic sodium ethoxide.<sup>256</sup>

Sodium cyanate, a reagent with a short shelf life, requiring frequent titration, has been used in cold, dilute acetic acid to convert *o*-aminoamides to 2-ureidobenzamides (**155**), which can be cyclized to quinazoline-2,4-diones (see **1**) by heating at 100°C with 7 *N* hydrochloric acid, 8 *N* sodium hydroxide,<sup>257</sup> or simply in water.<sup>258</sup> No yields were published. Ammonium thiocyanate, similarly acidified, was used to convert 2-aminothiophene-3-carboxamide to 2-thioxothieno[2,3-*d*]pyrimidin-4-ones (see **12**).<sup>255</sup>

Methyl isocyanate and 3-methyl-4-aminoimidazole-5-carboxamide, refluxed for 2 hr in pyridine, gave 9-methyl-1-thioxopurin-6-one (see **19**) (no yield given).<sup>259</sup> Phenyl isocyanate and 2-amino-5,6-diphenylpyrazine-3-carboxamide, set aside in pyridine for 3 days, gave a moderate yield of 3,6,7-triphenylpteridine-2,4-dione (see **10**).<sup>260</sup>

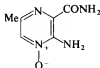
Phosgene, complexed with pyridine,<sup>261</sup> and 6-amino-1,2,4-triazine-5-carboxamide, warmed in dioxane, gave a moderate yield of pyrimidino[5,4-*e*]-*as*-triazine (**157**).<sup>262</sup> Thiophosgene acted on 1-methyl-4-methylaminoimidazole-5-(*N*-methyl)carboxamide to produce, not a thioxopurinone as had been claimed earlier, but an imidazo[4,5-*d*][1,3]thiazine.<sup>263</sup>



(157)



(158)



(159)

Ethyl chloroformate, like urea, is frequently used for converting *o*-aminoamides to annelated pyrimidine-2,4-diones. It was introduced in 1889 by Abt, who mixed 2-aminobenzamide and ethyl chloroformate in ether, then heated the resulting ethoxycarbonylaminobenzamide (**158**) above its melting point to obtain quinazoline-2,4-dione (no yield given).<sup>250</sup> Since then, it has become customary either to boil the starting materials together, without solvent, or to stir them in cold pyridine, which assists the reaction. The

<sup>256</sup> K. Hartke, A. Alarcon, D. Ramirez, and J. Bartulin, *Arch. Pharm. (Weinheim, Ger.)* **229**, 914 (1966) [*CA* 66, 46395 (1967)].

<sup>257</sup> F. H. S. Curd, J. K. Landquist, and F. L. Rose, *J. Chem. Soc.*, 1759 (1948).

<sup>258</sup> W. A. Jacobs and M. Heidelberger, *J. Am. Chem. Soc.* **39**, 2418 (1917).

<sup>259</sup> A. H. Cook and E. Smith, *J. Chem. Soc.*, 3001 (1949).

<sup>260</sup> E. C. Taylor, R. B. Garland, and C. F. Howell, *J. Am. Chem. Soc.* **78**, 210 (1956).

<sup>261</sup> C. Scholtissek, *Chem. Ber.* **89**, 2562 (1956).

<sup>262</sup> C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Heterocycl. Chem.* **5**, 581 (1968).

<sup>263</sup> R. Walentowski and H.-W. Wanzlick, *Chem. Ber.* **102**, 3000 (1969).



urethane is then usually cyclized in boiling ethanolic sodium ethoxide. The overall yields vary from good to excellent. The two reactions can be made to take place consecutively in one vessel by boiling the two starting materials with potassium carbonate in dioxane (4 hr for up to 2 days), with overall yields ranging from moderate to good.<sup>264,265</sup>

The following examples illustrate the scope of this reaction: 3-aminopyrrole-2-carboxamide to a pyrrolo[3,2-*d*]pyrimidine-2,4-dione<sup>205</sup>; 2-amino(*N*-alkyl)benzamides to 3-alkyl-2,4-quinazoline-2,4-diones<sup>266</sup>; 5-aminothiazole-4-carboxamide to thiazolo[5,4-*d*]pyrimidine-2,4-dione (see **149**)<sup>236</sup>; 4-aminoimidazole-5-carboxamide (and derivatives) to purine-2,6-diones (see **19**)<sup>264,265</sup>; and 2-aminopyridine-3-carboxamide (and its *C*-alkyl derivatives) to correspondingly substituted pyrido[2,3-*d*]pyrimidine-2,4-diones (see **3**).<sup>267</sup> Whereas 2-aminopyrazine-3-carboxamide (see **9**) (which does not react with urea at 150°C) was unchanged by ethyl chloroformate and potassium carbonate in refluxing dioxane,<sup>127</sup> the related 2-amino-5,6-diphenylpyrazine-3-(*N*-benzyl)carboxamide, when refluxed in excess ethyl chloroformate for 20 hr gave an excellent yield of the urethane.<sup>229</sup> Moreover, 2-amino-3-aminocarbonyl-5-methylpyrazine 1-oxide (**159**), boiled for 4 hr with ethyl chloroformate, gave the expected urethane, which methanolic sodium methoxide converted to 6-methyl-2,4-dioxopteridine 8-oxide in excellent overall yield.<sup>242</sup>

Phenyl thiochloroformate (ClCOSPh) has been used to produce purine-2,6-diones in good yields from 4-aminoimidazole-5-carboxamide and its derivatives; phenylmercaptan is evolved.<sup>201</sup>

Diethyl carbonate in boiling ethanolic sodium ethoxide has occasionally been used to convert *o*-aminoamides to annelated pyrimidine-2,4-diones—for example, 2-amino-5-cyanopyridine-3-carboxamide to 6-cyanopyrido[2,3-*d*]pyrimidine-2,4-dione (see **3**)<sup>245</sup>; 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide to 9-benzyl-8-azapurine-2,6-dione (see **21**)<sup>268</sup>; 4-amino-3-ribofuranosidoimidazole-5-carboxamide to 9-ribofuranosidopurine-2,6-dione (xanthosine) (see **19**)<sup>269</sup>; and 1,2,4-triazine-6-carboxamide to 3-aminopyrimidino[4,5-*e*]-1,2,4-triazine-6,8-dione (see **157**).<sup>270</sup> Refluxing times varied from 1 hr to 4 days, and yields from moderate to excellent.

Carbon disulfide in conjunction with a base has furnished a few examples of the conversion of an *o*-aminoamide to an annelated 2-thioxo-

<sup>264</sup> F. G. Mann and J. W. Porter, *J. Chem. Soc.*, 751 (1945).

<sup>265</sup> F. F. Blicke and H. C. Godt, *J. Am. Chem. Soc.* **76**, 3653 (1954).

<sup>266</sup> S. M. Gadekar, A. M. Kotsen, and E. Cohen, *J. Chem. Soc.*, 4666 (1964).

<sup>267</sup> A. Dornow and O. Hahmann, *Arch. Pharm. (Weinheim, Ger.)* **290**, 61 (1957).

<sup>268</sup> H. Bredereck and W. Baumann, *Justus Liebigs Ann. Chem.* **701**, 143 (1967).

<sup>269</sup> A. Yamazaki, I. Kumashiro, and T. Takenishi, *J. Org. Chem.* **32**, 3032, 3258 (1967).

<sup>270</sup> E. C. Taylor and R. W. Morrison, *J. Am. Chem. Soc.* **87**, 1976 (1965).

pyrimidin-4-one. The yields varied from good to excellent. Thus, 4-amino-3-methylimidazole-5-carboxamide, in refluxing pyridine (12 hr) gave 2-thioxo-9-methylpurin-6-one (see **19**),<sup>201</sup> and *o*-amino(*N*-alkyl)benzamides in boiling ethanolic sodium hydroxide furnished 3-alkyl-2-thioxoquinazolin-4-ones.<sup>271</sup> The reaction can be intensified by using potassium *O*-ethyl dithiocarbonate (xanthogenate) (EtOCS<sub>2</sub>K)<sup>188</sup> in place of carbon disulfide in refluxing pyridine or dimethylformamide. Thus, 3-amino-4-ethoxycarbonyl-5-methyl-2-methylaminocarbonylpyrrole gave 7-ethoxycarbonyl-3,6-dimethyl-2-thioxopyrrolo[3,2-*d*]pyrimidin-4-one (see **14**),<sup>205</sup> and 4-aminoimidazole-5-carboxamide produced 2-thioxopurin-6-one.<sup>269</sup>

### 7. With Aldehydes or Ketones

*o*-Aminoamides have been condensed with aldehydes to give annelated 1,2-dihydropyrimidin-4-ones. Thus, 2-aminobenzamide, boiled for 30 mins in aqueous ethanol with formaldehyde and sodium hydroxide, gave an excellent yield of 1,2-dihydroquinazolin-4-one (see **1**). The corresponding 2-methylaminoamide similarly produced the 2-methyl homolog (see **1**).<sup>272</sup> Both *cis*- and *trans*-2-aminocyclohexanecarboxamides, set aside in aqueous formaldehyde, produced moderate yields of the corresponding isomers of 1,2,4a,5,6,7,8,8a-octahydroquinazolin-4-one.<sup>61</sup> Again, 2-amino(*N*-4-bromophenyl)benzamide, briefly warmed with formaldehyde and sodium hydroxide in ethanol, gave an excellent yield of 3-*p*-bromophenyl-1,2-dihydroquinazolin-4-one. Amides with several other aromatic substituents were also successful.<sup>273</sup>

Methylenebispyridine was used as a source of formaldehyde to convert 2-aminobenzene-carboxanilide to 3-phenyl-1,2-dihydroquinazolin-4-one in excellent yield.<sup>273</sup>

2-Aminobenzamide and *o*-anisaldehyde, refluxed briefly in ethanol, gave an anil, which, when heated in 2 *N* sodium hydroxide for 30 mins, furnished an excellent yield of 2-*o*-methoxyphenyl-1,2-dihydroquinazolin-4-one. Several other aromatic aldehydes reacted similarly.<sup>274</sup> Various aromatic aldehydes reacted with 2-alkylaminobenzamides in boiling ethanol containing hydrogen chloride to give excellent yields of 1-aryl-1,2-dihydroquinazolin-4-one.<sup>275</sup>

<sup>271</sup> N. Kaur, I. Singh, and H. Singh, *Indian J. Chem.* **1**, 308 (1963).

<sup>272</sup> G. Pala and A. Mantegani, *Gazz. Chim. Ital.* **94**, 595 (1964).

<sup>273</sup> J. R. Feldman and E. C. Wagner, *J. Org. Chem.* **7**, 31 (1942).

<sup>274</sup> T. A. K. Smith and H. Stephen, *Tetrahedron* **1**, 38 (1957).

<sup>275</sup> H. Gurien and B. B. Brown, *J. Pharm. Sci.* **52**, 1102 (1963).

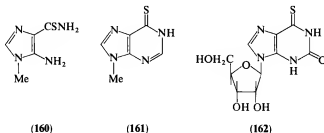
Finally, acetone and 2-aminobenzamide, refluxed 15 hr in 1 *N* hydrochloric acid, produced 2,3-dimethyl-1,2-dihydroquinazolin-4-one (no yield given).<sup>276</sup> Apparently, aldehydes and ketones have yet to be tried on a  $\pi$ -deficient host ring.

### B. FROM AMIDES (FOR 4-AMINOPYRIMIDINES)

In this important reaction, which provides the only known means of converting *o*-aminoamides to annelated 4-aminopyrimidines, the amide is acted on with dimethylformamide and phosphoryl chloride; the product, a cyanodimethylaminomethyleneamino derivative (see **118**), is then cyclized with ammonia or an amine (see Section VI,A,4, where it is treated as a reaction of an *o*-aminonitrile).

### C. FROM THIOAMIDES (FOR PYRIMIDIN-4-THIONES)

*o*-Aminothioamides are readily obtained by the action of phosphorus pentasulfide and pyridine on the amides<sup>229</sup> or by the reaction between *o*-aminonitriles and hydrogen sulfide in the presence of triethylamine.<sup>179</sup> They take part in many of the same cyclization reactions as the *o*-aminoamides, yet have been relatively overlooked.



Examples of ring closure leading to an annelated pyrimidine-4-thione in which the 2-position is unsubstituted will now be given. 4-Amino-3-methylimidazole-5-thiocarboxamide (**160**) was converted to the 4-formamido analog by acetic formic anhydride at 100°C; this amide cyclized to 9-methylpurin-6-thione (**161**) when boiled for 2 hr with 0.05 *N* potassium bicarbonate (good overall yield).<sup>136</sup> The lower homolog, 4-formamidoimidazole-5-carboxamide did not cyclize with this reagent,<sup>136</sup> but boiling for 10 mins

<sup>276</sup> H. C. Carrington, *J. Chem. Soc.*, 2527 (1955).

with 0.5 *N* sodium hydroxide gave an excellent result<sup>277</sup>; a change of reagent to ethyl formate in ethanolic sodium ethoxide (1.5 hr boiling) made it possible for both stages to proceed as though one (excellent yield).<sup>277</sup> An inviting alternative is to heat 4-aminoimidazole-5-thiocarboxamide with formamide at 200°C for 1 hr, although no yield was given.<sup>278</sup> 2-Aminopyrazine-2-thiocarboxamide (see 9), when heated with triethyl orthoformate and acetic anhydride for 2 hr (bath at 145°C), produced an excellent yield of pteridine-4-thione.<sup>127</sup> The 5,6-diphenyl analog of this pyrazine behaved similarly, as did the 3-(*N*-butyl) derivative of the latter.<sup>229</sup>

Examples in which the 2-position of the annelated pyrimidine is substituted include the following. 2-Aminopyrazine-3-thiocarboxamide and trifluoroacetamide, boiled in ethanolic sodium ethoxide for 8 hr, produced a good yield of 4-mercapto-2-trifluoromethylpteridine (the HS— nature of the sulfur substituent was verified by <sup>1</sup>H NMR)<sup>213</sup>; fusion of 4-aminoimidazole-5-thiocarboxamide with urea (160°C, 1.5 hr) provided 6-thioxopurin-2-one in excellent yield<sup>277</sup>; 4-amino-3-ribofuranosidoimidazole-5-thiocarboxamide and diethyl carbonate gave 6-thioxo-9-ribofuranosidopurin-2-one (**162**) in good yield<sup>277</sup>; 2-amino-5,6-diphenylpyrazine-3-(*N*-butylthiocarboxamide) and ethyl chloroformate, refluxed for 20 hr, provided the urethane, which was cyclized by 0.6 *N* sodium hydroxide in good overall yield.<sup>229</sup>

Finally, 2-aminothiobenzamide and acetone, in boiling 1 *N* hydrochloric acid, furnished an excellent yield of 2,2-dimethyl-1,2-dihydroquinazoline-4-thione (see 1).<sup>276</sup>

### VIII. From Rings with an Amino Group Adjacent to a Carboxylic Acid or an Ester Group (for Pyrimidin-4-ones)

Because *o*-aminocarboxylic acids and their esters lack the nitrogen atom of the *o*-aminoamides, fewer reagents are available for their cyclization.

#### A. FROM ACIDS

The *o*-amino acids have two possible disadvantages. They may decarboxylate faster than they can react (2-aminobenzoic acid slowly loses carbon dioxide at 150°C), and they tend to combine with bases present at any stage of the reaction. In spite of this, they have been the subject of many

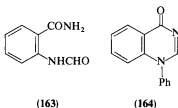
<sup>277</sup> A. Yamazaki, I. Kumashiro, T. Takenishi, and M. Ikehara, *Chem. Pharm. Bull.* **16**, 2172 (1968).

<sup>278</sup> G. H. Hitchings and G. B. Elion, U.S. Patent 2,756,228 (1956) [*CA* **51**, 2887 (1957)].

publications, most of which describe syntheses of quinazolin-4-ones. Isatoic anhydride (119), although formally related to the *o*-amino acids, has been reserved for Section XI (starting materials that require preliminary rearrangement).

### 1. With Formamide

In 1895, Niementowski discovered the reaction that still bears his name: the condensation of 2-aminobenzoic acid (anthranilic acid) with formamide to give quinazolin-4-one. He used two molecular equivalents of formamide and heated at 125°C for 3 hr.<sup>279</sup> The yield is excellent, even on the 500 g scale.<sup>280</sup> The reaction also goes well when the benzene ring is substituted, whether by electron-attracting or electron-releasing substituents.<sup>1</sup> The course of the reaction is as follows.<sup>281,282</sup> Ammonium-2-formamidobenzoic acid is first formed and can be isolated when the reaction is run at a lower temperature. At 130°C, this salt is dehydrated to 2-formamidobenzamide (163), which slowly cyclizes to quinazolin-4-one.



Attempts have been made to improve yields by (a) starting with the pre-formed ammonium salt,<sup>283</sup> (b) doubling the proportion of formamide,<sup>282</sup> or (c) running the reaction at a low and then a higher temperature.<sup>282,284</sup> Seventeen C-substituted anthranilic acids were converted to quinazolin-4-ones by heating at 130°C for 45 min, then at 175°C for 75 min, and the yields were excellent.<sup>284</sup>

Whether annelated pyrimidin-4-ones should be made from *o*-aminoamides or from *o*-amino acids depends on the availability of each. The former gives a wider variety of reactions, and the reactions common to both host molecules seem to proceed faster and cleaner with the amides. However, if the amide

<sup>279</sup> S. Niementowski, *J. Prakt. Chem.*, [2] **51**, 564 (1895).

<sup>280</sup> W. L. F. Armarego, *J. Appl. Chem.* **11**, 70 (1961).

<sup>281</sup> M. T. Bogert and A. H. Gotthelf, *J. Am. Chem. Soc.* **22**, 522 (1900).

<sup>282</sup> J. F. Meyer and E. C. Wagner, *J. Org. Chem.* **8**, 239 (1943).

<sup>283</sup> M. T. Bogert and V. J. Chambers, *J. Am. Chem. Soc.* **27**, 649 (1905).

<sup>284</sup> B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.* **17**, 141 (1952).

has to be made separately from the acid, it is often more economical to use the Niementowski amino acid reaction.

The Niementowski reaction has not been widely used for heterocyclic host molecules. The following examples comprise most of what has been done, mainly at 170°C for 2 hr (good yields): pyrido[2,3-*d*]pyrimidin-4-one (see 3) from 2-aminopyridine-3-carboxylic acid<sup>285,286</sup>; pyrido[3,2-*d*]pyrimidin-4-one (see 6) from 3-aminopyridine-2-carboxylic acid<sup>216,287</sup>; and pyrido[3,4-*d*]pyrimidin-4-one (see 4) from 3-aminopyridine-4-carboxylic acid.<sup>288,289</sup>

*N*-Methylformamide converted 2-aminopyridine-3-carboxylic acid to 3-methylpyrido[2,3-*d*]pyrimidin-4-one (5 hr at 180°C) in good yield.<sup>290</sup> The same reagent also made 3-methyl-6-nitroquinazolin-4-one from 2-amino-5-nitrobenzoic acid in excellent yield; some slowly reacting 2-aminobenzoic acids were assisted with phosphoryl chloride.<sup>291</sup> A moderate yield of 3-phenylquinazolin-4-one was obtained from the action of formamide on 2-aminobenzoic acid (90 min at 140°C).<sup>282</sup>

The unexpected reducing power of formamide was discovered when 2-aminobenzoic acid and that amide were refluxed for 4 hr, giving 2,3-dihydro-1-phenylquinazolin-4-one (*m/e* 224) instead of 164. The latter was dihydrogenated when boiled with formamide.<sup>292</sup> The presence of an isolated double bond in 164 and the severe conditions should explain the result.

## 2. With Other Amides, Nitriles, or Imidates

Niementowski found that no other amide reacted so freely with *o*-aminoamides as did formamide and that the difficulty increased with each carbon atom added to the acyl group.<sup>279</sup> To introduce a *C*-aryl substituent, it is preferable to heat an *o*-acylamino acid with formamide. Thus, 2-benzamidobenzoic acid, in formamide at 160°C for 3 hr, gave a good yield of 2-phenylquinazolin-4-one.<sup>293</sup> However, the use of formamide to condense 2-acetamidobenzoic acid resulted in a mixture of two products, one with

<sup>285</sup> L. Klisjecki and E. Sucharda, *Rocz. Chem.* **3**, 251 (1923).

<sup>286</sup> R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.* **77**, 2256 (1955).

<sup>287</sup> A. Albert and A. Hampton, *J. Chem. Soc.*, 505 (1954).

<sup>288</sup> S. Gabriel and J. Colman, *Ber. Dtsch. Chem. Ges.* **35**, 2831 (1902).

<sup>289</sup> I. R. Gelling and D. G. Wibberley, *J. Chem. Soc. C*, 931 (1969).

<sup>290</sup> E. H. Rizkalla, A. D. Brown, M. G. Stout, and R. K. Robins, *J. Org. Chem.* **37**, 3975 (1972).

<sup>291</sup> K. Tsuda, S. Fukushima, H. Ichikawa, S. Yoshida, and G. Ishia, *Yakugaku Zasshi* **62**, 69 (1942) [*CA* **45**, 1580 (1951)].

<sup>292</sup> W. J. Irwin, *J. C. S. Perkin I*, 353 (1970).

<sup>293</sup> V. S. Patel and S. R. Patel, *J. Indian Chem. Soc.* **42**, 531 (1965).

methyl and one with hydrogen in the 2-position of the quinazoline.<sup>294</sup> (A similar mixture was reported for the condensation of 2-aminopyridine-3-carboxamide with acetamide.<sup>285</sup>) However, heating 2-acetamidobenzoic acid with acetamide gave a good yield of 2-methylquinazolin-4-one (3 hr, 185°C).<sup>294</sup>

Thioamides, which react much more vigorously than amides, provide the best solution to the problem of preparing 2-substituted quinazolin-4-ones. Thus, thioacetamide and anthranilic acid gave an excellent yield of 2-methylquinazolin-4-one when fused together at 155°C for 30 min,<sup>295</sup> and thiobenzamide gave a quantitative yield of the 2-phenyl analog (160°C, 2 hr).<sup>296</sup>

Nitriles and imidates have found little use, so far. Heating propionitrile and 2-aminobenzoic acid at 210°C in a closed vessel gave only a low yield of 2-methylquinazolin-4-one.<sup>297</sup> Anthranilic acid and 10 of its C-substituted derivatives were refluxed (5–50 hr) with ethyl acetimidate and benzimidate in methanol to give 2-methyl- and 2-phenylquinazolin-4-ones, respectively, in moderate yields; three aminopyridine carboxylic acids behaved similarly.<sup>298</sup> *N*-Phenylbenzimidoyl chloride [ $\text{PhC(NPh)Cl}$ ] and ammonium 2-aminobenzoate, in cold acetone, produced 2,3-diphenylquinazolin-4-one in good yield.<sup>299</sup>

### 3. With Ammonia or Amines (on *o*-Acylamino Acids)

Reactions of this kind were introduced when Bogert and Hand heated 2-aminobenzoic acid with acetic anhydride in the presence of ammonium carbonate and obtained a low yield of 2-methylquinazolin-4-one (see 1).<sup>300</sup> In stages, this reaction was developed to give annelated pyrimidin-4-ones bearing alkyl or aryl groups in both the 2- and 3-positions (see Scheme 2).

3-Acetamidopyridine-2-carboxylic acid, when refluxed with acetic anhydride for 90 min, gave an excellent yield of 2-methylpyrido[3,2-*d*][1,3]-oxazin-4-one (**165**). At room temperature this is immediately converted to pyridines of the type **166** by ammonia, aliphatic or aromatic amines, hydroxylamine, or hydrazine. These products spontaneously cyclize to the pyrido-[3,2-*d*]pyrimidin-4-ones **167** in excellent overall yields. When the starting material is 3-benzamidopyridine-2-carboxylic acid, the ring-opened stage (analogous to **166**) is stable and requires phosphoryl chloride to cyclize it

<sup>294</sup> H. J. Mehta, V. S. Patel, and S. R. Patel, *J. Indian Chem. Soc.* **47**, 125 (1970).

<sup>295</sup> A. B. Sen and S. K. Gupta, *J. Indian Chem. Soc.* **39**, 368 (1962).

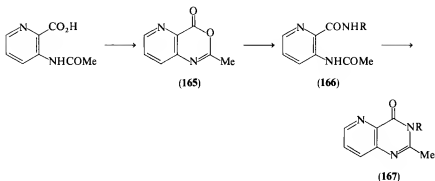
<sup>296</sup> B. Paweleski, *Ber. Dtsch. Chem. Ges.* **36**, 2384 (1903).

<sup>297</sup> A. H. Gotthelf, *J. Am. Chem. Soc.* **23**, 611 (1901).

<sup>298</sup> W. Ried and J. Valentin, *Justus Liebigs Ann. Chem.* **707**, 250 (1967).

<sup>299</sup> P. R. Levy and H. Stephen, *J. Chem. Soc.*, 985 (1956).

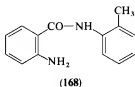
<sup>300</sup> M. T. Bogert and W. F. Hand, *J. Am. Chem. Soc.* **28**, 94 (1906).



SCHEME 2

to the equivalent of **167**.<sup>301</sup> 3-Aminopyridine-4-carboxylic acid gave similar reactions.<sup>289</sup>

Similar syntheses can be carried out in one vessel by heating 2-acetamidobenzoic acid with an aliphatic or aromatic amine and phosphorus trichloride (2 hr in toluene), giving 2-methyl-3-alkyl- or 2-methyl-3-arylquinazolin-4-ones in excellent yields.<sup>302</sup> The intermediate, with aniline, may be phenylphosphazooanilide ( $\text{PhN}-\text{P}-\text{NHPh}$ ) because this condenses with 2-acetamidobenzoic acid in boiling toluene with equally good results.<sup>302</sup> This reaction, which is used to make the hypnotic drug methaqualone, 2-methyl-3-(2-methylphenyl)quinazolin-4-one, has produced several variations, e.g., in which the phosphorus halide is replaced by polyphosphoric acid<sup>303</sup> or the starting material is so chosen (as with **168**) that the upper part of the ring is closed first.<sup>304</sup>



3-Acetamidothiophene-2-carboxylic acid, condensed with aniline and phosphorus trichloride, gave only a low yield of 2-methyl-3-phenylthieno-[3,2-*d*]pyrimidin-4-one (see **14**).<sup>305</sup>

<sup>301</sup> W. J. Irvin and D. G. Wibberley, *J. Chem. Soc.*, 4240 (1965).

<sup>302</sup> H. W. Grimmel, A. Guenther, and J. F. Morgan, *J. Am. Chem. Soc.* **68**, 542 (1946).

<sup>303</sup> P. A. Petyunin and Yu. V. Kozhevnikov, *Med. Prom. SSSR* **20**, 13 (1966) [*CA* **65**, 7176 (1966)].

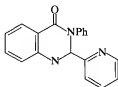
<sup>304</sup> J. Tani, Y. Yamada, T. Oine, T. Ochiai, R. Ishida, and I. Inoue, *J. Med. Chem.* **22**, 95 (1979).

<sup>305</sup> W. Ried and E. Kahn, *Justus Liebigs Ann. Chem.* **716**, 219 (1968).



#### 4. With Amidines or Guanidine

These reagents have not been used frequently, but the following examples suggest their potentialities. 2-Aminobenzoic acid and *N,N'*-diphenylformamidine, when refluxed for 45 min at 155°C, gave 3-phenylquinazolin-4-one in moderate yield (with evolution of aniline),<sup>282</sup> and *N,N'*-diphenylpyridine-2-carboxamide produced 3-phenyl-2-(2-pyridyl)quinazolin-4-one (**169**).<sup>306</sup> Guanidine carbonate and 3-aminopyridine-2-carboxylic acid, fused for 4 hr at 170°C, provided 2-aminopyrido[3,2-*d*]pyrimidin-4-one (see **6**) in moderate yield.<sup>249</sup> *trans*-2-Aminocyclohexanecarboxylic acid, when stirred at 20°C for 3 days with *S*-methylisothiuronium sulfate in 8 *N* sodium hydroxide, gave an excellent yield of *trans*-2-guanidinocyclohexanecarboxylic acid, which boiling ethanolic hydrogen chloride converted, quantitatively, to 2-amino-4a,5,6,7,8,8a-hexahydroquinazolin-4-one. The *cis* analog was made similarly, but fusing the amino acid with cyanamide provided a smaller yield of it.<sup>61</sup>



(169)

#### 5. With Urea or Isocyanates and Their Sulfur Analogs

In 1872, Griess fused urea and 2-aminobenzoic acid and, although unaware of the nature of his product, had made quinazoline-2,4-dione. Since that time, the reaction has been frequently used for converting C-substituted 2-aminobenzoic acids to their corresponding quinazoline-2,4-diones in excellent yields, usually at 190°–200°C maintained for 1–5 hr.<sup>307,308</sup> In addition, 2-aminopyridine-3-carboxylic acid and urea, slowly heated to 210°C, gave a good yield of pyrido[2,3-*d*]pyrimidine-2,4-dione.<sup>286</sup> Pyrido[3,4-*d*]pyrimidine-2,4-dione was formed similarly (yield not given).<sup>288</sup>

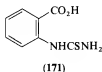
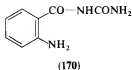
A simple, but seldom electronically favored approach is to boil the aminobenzoic acid and urea in water for a day; this gave for the 5-nitro

<sup>306</sup> T. Hisano, T. Nishi, and M. Ichikawa, *Yakugaku Zasshi* **92**, 582 (1972) [*CA* **77**, 101519 (1972)].

<sup>307</sup> E. H. Huntress and J. V. K. Gladding, *J. Am. Chem. Soc.* **64**, 2644 (1942).

<sup>308</sup> V. Oakes, H. N. Rydon, and K. Undheim *J. Chem. Soc.*, 4678 (1962).

acid a moderate yield of 7-nitroquinazoline-2,4-dione.<sup>257</sup> In an alternative approach, 2-aminobenzoylurea (**170**) was heated with dilute sulfuric acid at 100°C to furnish quinazolin-4-one (no yield given).<sup>309</sup>



Thiourea, although a successful reagent for the *o*-aminoamides, has yet to establish itself in the *o*-amino acid series. Of the few known examples of its use, 2-aminobenzoic acid and thiourea at 170°C gave 2-thioxoquinazolin-4-one,<sup>310</sup> and *N*-phenylthiourea produced the 3-phenyl derivative<sup>311</sup> in unstated (but apparently low) yields. Again, 2-aminopyridine-3-carboxylic acid and thiourea, at 210°C for only 5 min, gave a low yield of 2-thioxopyrido[2,3-*d*]pyrimidin-4-one (see 3).<sup>286</sup>

Sodium and potassium cyanates, provided that attention is paid to their short shelf life (Section VII,A,6), offer an attractive alternative to fusion with urea for preparing annelated pyrimidine-2,4-diones. In the *Organic Syntheses* preparation of quinazoline-2,4-dione, anthranilic acid and potassium cyanate in cold dilute acetic acid were converted (in 20 min) to 2-ureidobenzoic acid, which cold aqueous sodium hydroxide cyclized to the quinazolinone in excellent overall yield.<sup>312</sup> Alternatively, the ring of a ureidobenzoic acid may be closed with hot, dilute hydrochloric acid.<sup>257</sup> Ring closure of similar ureides in the pyridine series has required heating at 210°–240°C, often for as long as 3 hr.<sup>249,267</sup> An even more  $\pi$ -deficient example, 2-aminopyrazine-3-carboxylic acid, did not react with sodium cyanate in dilute acid or with boiling urethane.<sup>127</sup>

Ammonium thiocyanate and anthranilic acid, heated at 180°C for 30 min, gave an excellent yield of 2-thioxoquinazolin-4-one, and several C-substituted acids behaved similarly.<sup>313</sup> Alternatively, this thiocyanate may be

<sup>309</sup> O. Diels and A. Wagner, *Ber. Dtsch. Chem. Ges.* **45**, 874 (1912).

<sup>310</sup> A. Stewart, *J. Prakt. Chem.* [2] **44**, 415 (1891).

<sup>311</sup> B. Pawelewski, *Ber. Dtsch. Chem. Ges.* **38**, 130 (1905).

<sup>312</sup> N. A. Lange and F. E. Sheibley, *Org. Synth., Collect. Vol.* **2**, 79 (1943).

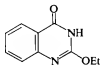
<sup>313</sup> N. K. Ralhan and H. S. Sachdev, *J. Sci. Ind. Res., Sect. B* **19**, 215 (1960).

used in cold, dilute hydrochloric acid to furnish the thioureide **171**, which can be cyclized by heating at 180°C for, say, 3 hr.<sup>249</sup>

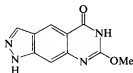
Phenyl isocyanate boiled with 2-methylaminobenzoic acid gave 1-methyl-3-phenylquinazoline-2,4-dione, but methyl isocyanate did not react. On the other hand, methyl isothiocyanate at 145°C (sealed vessel) produced 1,2-dimethyl-2-thioxoquinazolin-4-one, whereas phenyl isothiocyanate gave poor results (yields not stated).<sup>314</sup> Anthranilic acid heated with amyl isocyanate gave the ureide, which could be cyclized with acid or base<sup>315</sup>; however, potassium anthranilate, set aside overnight in ethanolic phenyl isocyanate, gave a moderate yield of 2-thioxo-3-phenylquinazolin-4-one directly.<sup>316</sup>

### 6. With Cyanogen and Its Derivatives

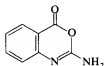
In 1869, cyanogen and anthranilic acid, when set aside in ethanol for a week, produced a mysterious substance,<sup>317</sup> which was later identified as 2-ethoxyquinazolin-4-one (**172**).<sup>318</sup> Somewhat similarly, 6-aminoindazole-5-carboxylic acid, when stirred with cyanogen in methanol for 5 hr at 0°C, was converted, in good yield, to 7-methoxypyrazolo[4,3-*g*]quinazolin-5-one (**173**).<sup>319</sup> In each case, the amino group in the starting material apparently became converted to an —NHC(NH)CN group.



(172)



(173)



(174)

Cyanogen bromide and sodium 2-aminobenzoate readily give 2-cyanaminobenzoic acid, which cyclizes spontaneously to 2-aminobenz[3,1]oxazin-4-one (**174**) (quantitative overall yield), which is converted by methylamine to 3-methylquinazoline-2,4-dione in two stages but in excellent yield. Arylamines behave similarly.<sup>316</sup>

<sup>314</sup> A. Weddige and G. Fortmann, *J. Prakt. Chem.* [2] **55**, 123 (1897).

<sup>315</sup> F. Russo and M. Ghelardoni, *Ann. Chim. (Rome)* **56**, 839 (1966).

<sup>316</sup> K. Lempert and G. Doleschall, *Monatsh. Chem.* **95**, 950 (1964); G. Doleschall and K. Lempert, *ibid.*, 1068.

<sup>317</sup> P. Griess, *Ber. Dtsch. Chem. Ges.* **2**, 415 (1869).

<sup>318</sup> H. Finger and H. Günzler, *J. Prakt. Chem.* [2] **83**, 198 (1911).

<sup>319</sup> E. Cuny, F. Lichtenthaler, and U. Jahn, *Chem. Ber.* **114**, 1624 (1981).

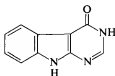
## B. FROM ESTERS

*o*-Amino esters have one advantage over *o*-amino acids in the preparation of annelated pyrimidines, namely, freedom from the tendency to decarboxylate. On the other hand, they have two disadvantages: increased volatility and poor affinity of the ester group to react with ammonia or an organic amine. It is remarkable that methyl anthranilate and ethanolic ammonia, in a sealed vessel at 100°C, formed no 2-aminobenzamide.<sup>282</sup> Only when an electron-attracting substituent is present in the host ring can one be sure that the ester group will react with ammonia as fast as the latter is produced, assuming normal open-vessel conditions.

## 1. With Formamide

Of the few examples of the use of this reagent, the following are typical. 4-Amino-5-methoxycarbonyl-3-phenyl-1,2,3-triazole (see **20**), boiled for 1 hr with formamide, gave 3-phenyl-8-azapurin-6-one (see **21**) in good yield, but the corresponding amide gave an excellent yield.<sup>217</sup> Again, 4-amino-3-ethoxycarbonylpyridine and formamide, after 3 hr at 210°C, produced a good yield of pyrido[4,3-*d*]pyrimidin-4-one (see **5**).<sup>320</sup>

$\pi$ -Excessive materials usually require an additive. Thus, 3-formamido-4-methoxycarbonylthiophene gave a good yield of thieno[3,4-*d*]pyrimidin-4-one (see **13**) when ammonium formate was added to the formamide,<sup>321</sup> and 2-amino-3-methoxycarbonylthiophene produced the corresponding thieno[2,3-*d*]pyrimidin-4-one similarly, in excellent yield.<sup>322</sup> Again, 2-amino-3-ethoxycarbonylindole and formamide gave an excellent yield of pyrimidino[4,5-*b*]indol-4-one (**175**), provided that sodium methoxide was also present.<sup>323</sup>



(175)

<sup>320</sup> E. C. Taylor, R. J. Knopf, J. A. Coglian, J. W. Barton, and W. Pfeleiderer, *J. Am. Chem. Soc.* **82**, 6058 (1960).

<sup>321</sup> B. R. Baker, J. P. Joseph, R. E. Schaub, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.* **18**, 138 (1953).

<sup>322</sup> M. Robba and J. M. Lecomte, *C. R. Hebd. Seances, Acad. Sci., Ser. C* **264**, 207 (1967).

<sup>323</sup> R. G. Glushkov, V. A. Volokova, and O. Yu. Maghidson, *Khim. Farm. Zh.* **1**, 25 (1967) [*CA* **68**, 105143 (1968)].

Finally, a mixture of formamide and acetic anhydride was needed to convert 2-amino-3-ethoxycarbonyl-1,4,5,6-tetrahydropyridine to 5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-4-one (moderate yield).<sup>324</sup>

## 2. With Nitriles or Imidates

Higher amides, as well as the nitriles, are poorly represented as reagents for converting *o*-amino esters to annelated pyrimidines. At least methyl anthranilate and ethyl cyanofornate (not usually a reactive chemical) formed a good yield of 2-ethoxycarbonylquinazolin-4-one (**140**) when heated at 120°C with hydrogen chloride in acetic acid.<sup>325</sup>

The imido esters have attracted more interest. 2-Phenylquinazolin-4-one has been made by combining methyl anthranilate with ethyl benzimidate [PhC(NH)OEt] in boiling ethanol, by fusion at 210°C,<sup>326</sup> by refluxing the ester with ethyl *N*-phenylformimidate in decalin,<sup>327</sup> or by setting it aside with *N*-(*p*-toluenesulfonyl)benzimidoyl chloride at room temperature,<sup>209</sup> the yields varying from moderate to excellent. Ethyl benzimidate heated with 2-amino-3-ethoxycarbonyl-4,5-dihydrofuran and polyphosphoric acid at 160°C gave a low yield of 2-phenyl-5,6-dihydrofuro[2,3-*d*] pyrimidin-4-one (**176**).<sup>328</sup>

Benzyl thioacetimidate and 4-amino-2-ethoxycarbonylpyrazole, in boiling pyridine, gave a quantitative yield of 5-methylpyrazolo[4,3-*d*]pyrimidin-7-one (see **17**).<sup>329</sup>



## 3. With Ammonia (on *o*-Acylamino Acids)

This type of reaction has not been well developed for esters, but the following examples are typical. 4-Acetamido-5-ethoxycarbonylpyridazine gave

<sup>324</sup> H. Wamhoff and L. Lichtenthaler, *Chem. Ber.* **111**, 2297 (1978).

<sup>325</sup> Y. Sugiyama, T. Sasaki, and N. Nagato, *J. Org. Chem.* **43**, 4485 (1978).

<sup>326</sup> H. Finger and H. Schupp, *J. Prakt. Chem.* [2] **74**, 154 (1906).

<sup>327</sup> C. Runti, C. Nisi, and L. Sindellari, *Ann. Chim. (Rome)* **51** 719 (1961) [*CA* **56**, 4762 (1962)].

<sup>328</sup> H. Wamhoff, *Chem. Ber.* **101**, 3377 (1968).

<sup>329</sup> T. Huynh-Dinh, A. Kolb, C. Gouyette, J. Igolen, and S. Tran-Dinh, *J. Org. Chem.* **40**, 2825 (1975).

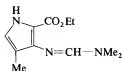
an excellent yield of 2-methylpyrimidino[4,5-*d*]pyridazin-4-one (see **150**) in cold ethanolic ammonia.<sup>240</sup> 3-Formamido-2-methoxycarbonylthiophene, in ethanolic ammonia at 120°C or with ammonium formate and formamide at 140°C, produced an excellent yield of thieno[3,2-*d*]pyrimidin-4-one (see **14**).<sup>330</sup>

2-Methylbenz[3,1]oxazin-4-one (acetylanthranil) (**177**), set aside at 25°C with ammonia in benzene, was quantitatively converted to 2-methylquinazolin-4-one. Slow as this reaction was in dry, apolar solvents, it became immensely faster when the solvent was undried; however, the product was then 2-acetamidobenzamide. Nevertheless, the reaction proceeded rapidly in pyridine, whether wet or dry, and the sole product was the quinazoline.<sup>331</sup>

3-Amino-2-ethoxycarbonyl-4-methylpyrrole was converted to the dimethylaminomethyleneamino analog (**178**) with dimethylformamide and phosphoryl chloride. The product, set aside for 3 days with cold methanolic ammonia, gave 7-methylpyrrolo[3,2-*d*]pyrimidin-4-one (**179**) in excellent yield.<sup>332</sup> The corresponding reaction with methyl anthranilate gave quinazolin-4-one quantitatively.<sup>333</sup>



(177)



(178)



(179)

#### 4. With Amidines or Guanidine

Most of the work described here has been done with guanidine. In one of the few amidine examples, methyl anthranilate and *N,N'*-diphenylformamidine gave 3-phenylquinazolin-4-one in excellent yield when heated at 155°C for 45 min. The authors state that the initial attack is on the amino group.<sup>282</sup>

A mixture of guanidine carbonate and methyl anthranilate, slowly raised to 200°C and kept there until no more ammonia was evolved, produced 2-aminoquinazolin-4-one (no yield stated).<sup>334</sup> 2-Amino-3-ethoxycarbonylpyridine-5-carboxylic acid, guanidine hydrochloride, and ethanolic sodium

<sup>330</sup> M. Robba, J. M. Lecomte, and M. C. Sevrécourt, *Bull. Soc. Chim. Fr.*, 3630 (1970).

<sup>331</sup> L. A. Errede, P. D. Martinucci, and J. J. McBrady, *J. Org. Chem.*, **45**, 3009 (1980).

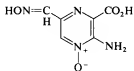
<sup>332</sup> M.-I. Lim, R. S. Klein, and J. J. Fox, *J. Org. Chem.*, **44**, 3826 (1979).

<sup>333</sup> Z. Csuros, R. Soos, J. Palinkas, and I. Bitter, Hungarian Patent Application 1498 (1968) [*CA* **74**, 141854 (1971)].

<sup>334</sup> F. Kunkell, *Ber. Dtsch. Chem. Ges.*, **38**, 1212 (1905).

ethoxide, after refluxing for 6 hr, provided 2-amino-4-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acid (see 3), quantitatively.<sup>245</sup> 4-Amino-5-ethoxycarbonylpyridazine and guanidine carbonate produced a good yield of 2-aminopyrimidino[4,5-*d*]pyridazin-4-one (see 150) when fused at 190°C.<sup>240</sup>

When 2-amino-3-carboethoxy-5-methylpyrazine 1-oxide (see 9) was refluxed with guanidine in methanolic sodium methoxide, a pyrazinoyl-guanidine was isolated [ $-\text{CONHC}(\text{NH})\text{NH}_2$ ]. Refluxing with dimethylformamide for 4 hr converted it to 2-amino-6-methyl-4-oxopteridine-8-oxide (see 10) in good overall yield.<sup>242</sup> In a unique demonstration of how to conserve an aldehyde function during annelation, 2-amino-3-ethoxycarbonyl-5-oximinomethylpyrazine 1-oxide (180) was refluxed with guanidine in methanolic sodium methoxide. The product, cyclized in boiling dimethylformamide, gave an excellent yield of 2-amino-6-oximino-4-oxopteridine 8-oxide.<sup>335</sup>



(180)

Some related reagents have also been tried. Alkyl and aryl cyanamides, prepared from alkyl or aryl ureas and benzenesulfonyl chloride, when set aside overnight in pyridine with methyl anthranilate, gave moderate yields of 3-alkyl- or 3-aryl-2-aminoquinazolin-4-ones.<sup>336</sup> *N,N'*-Diphenylisothio-uronium sulfate and methyl anthranilate, boiled together in nitrobenzene, produced 2-phenylamino-3-phenylquinazolin-4-one (no stated yield).<sup>337</sup> Dicyandiamide [ $\text{NCNHC}(\text{NH})\text{NH}_2$ ] and methyl anthranilate, in dilute hydrochloric acid, gave 2-guanidinoquinazolin-4-one.<sup>338</sup>

### 5. With Urea or Isocyanates and Their Sulfur Analogs

The synthesis of pyrimidinediones by the several reagents dealt with under this heading constitutes the principal current use of the *o*-amino esters. The less frequently used reagents are dealt with first, leading up to the organic isocyanates, which hold pride of place.

<sup>335</sup> E. C. Taylor and K. Lenard, *Justus Liebigs Ann. Chem.* **726**, 100 (1965).

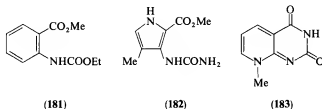
<sup>336</sup> R. J. Grout and M. W. Partridge, *J. Chem. Soc.*, 3540 (1960).

<sup>337</sup> J. F. Deck and F. B. Dains, *J. Am. Chem. Soc.* **55**, 4986 (1933).

<sup>338</sup> B. Skowronska-Serafinowa and T. Urbanski, *Rocz. Chem.* **26**, 51 (1952) [*CA* **47**, 7507 (1953)].

Urea and ethyl anthranilate, when refluxed in tetramethylene sulfone at 195°C, gave a good yield of quinazoline-2,4-dione, whereas thiourea produced only a moderate yield of 2-thioxoquinazolin-4-one.<sup>339</sup> 2-Amino-3-methoxycarbonylthiophene, when fused with urea, furnished thieno[2,3-*d*]pyrimidine-2,4-dione (see **12**) in good yield.<sup>340</sup>

Ethyl chloroformate and methyl anthranilate, heated 15 hr at 100°C, were converted quantitatively to methyl 2-ethoxycarbonyl aminobenzoate (**181**), which was converted to quinazoline-2,4-dione in excellent yield by heating in ethanolamine for 40 min at 160°C.<sup>341</sup> Urethane (ethyl aminocarbonate) and ethyl *N*-phenylanthranilate, when heated at 220°C for 1 hr, gave an excellent yield of 1-phenylquinazoline-2,4-dione.<sup>342</sup>



In the pyrrole series, in which the presence of the destabilizing amino group is better avoided, it has been shown that the ureide **182** can be made by Curtius rearrangement of the corresponding 3-carboxyazide. This ureide was converted to 7-methylpyrrolo[3,2-*d*]pyrimidine-2,4-dione (see **14**) in good yield when refluxed in methanolic sodium methoxide for 5 min. 5-Methylpyrrolo[2,3-*d*]pyrimidine-2,4-dione (see **12**) was similarly made from 3-ethoxycarbonyl-4-methyl-2-ureidopyrrole.<sup>343</sup>

Potassium cyanate and methyl 3-methoxyanthranilate, left in cold, acidified aqueous solution overnight, deposited methyl 2-ureido-3-methoxybenzoate, which, when boiled with water, cyclized to 8-methoxyquinazoline-2,4-dione; methyl 5-chloroanthranilate behaved similarly (no yields stated).<sup>257</sup> 2-Amino-3-ethoxycarbonyl-*N*-methylpyridinium iodide, refluxed for 24 hr with potassium cyanate in dilute acetic acid, was converted in good yield to 8-methylpyrido[2,3-*d*]pyrimidine (**183**).<sup>344</sup>

<sup>339</sup> J. B. Hynes, W. T. Ashton, H. G. Merriman, and F. C. Walker, *J. Med. Chem.* **17**, 682 (1974).

<sup>340</sup> M. Robba, J. M. Lecomte, and M. C. Sevracourt, *C. R. Hebd. Seances Acad. Sci., Ser. C* **266**, 128 (1968).

<sup>341</sup> R. J. Grout and M. W. Partridge, *J. Chem. Soc.*, 3546 (1960).

<sup>342</sup> B. Das and R. Mukherjee, *J. Indian Chem. Soc.* **40**, 35 (1963).

<sup>343</sup> M. T. Garcia-López, F. G. de las Heras, and M. Stud, *J. C. S. Perkin I*, 483 (1978).

<sup>344</sup> B. H. Rizkalla, A. D. Broom, M. G. Stout, and R. K. Robins, *J. Org. Chem.* **37**, 3975 (1972).



Potassium thiocyanate and methyl anthranilate, boiled in water for 40 hours, gave 2-thioxoquinazolin-4-one (no stated yield).<sup>345</sup>

Several organic isocyanates (methyl, butyl, cyclohexyl, benzyl, phenyl, and 1-naphthyl) gave correspondingly substituted methyl 2-ureidobenzoates when refluxed with methyl anthranilate in light petroleum for 18 hr. These ureides were cyclized by aqueous ethanolic hydrochloric acid to the appropriate 3-alkyl or 3-arylquinazoline-2,4-diones in excellent overall yields.<sup>346</sup> 2-Amino-3-methoxycarbonylpyridine, refluxed in pyridine with methyl isocyanate, gave 3-methylpyrido[2,3-*d*]pyrimidine-2,4-dione (see 3) directly in excellent yield.<sup>344</sup> 2-Amino-3-ethoxycarbonyl-4,6-dimethylpyridine and phenyl isocyanate, in toluene, gave a good yield of the ureide, which was converted to 5,7-dimethyl-3-phenylpyrido[2,3-*d*]pyrimidine-2,4-dione in excellent yield by heating at 180°C for 2 hr.<sup>235</sup>

3-Amino-2-ethoxycarbonyl-4-methylpyrrole and methyl isocyanate gave the ureide, which was cyclized by potassium carbonate in methanol to give an excellent yield of 3,7-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4-dione (see 14).<sup>332</sup> 3-Amino-2-*tert*-butoxycarbonyl-4-ethoxycarbonyl-5-methylpyrrole and butyl isocyanate, in boiling acetonitrile, produced 3-butyl-7-*tert*-butoxycarbonyl-5-methylpyrrolo[3,4-*d*]pyrimidine-2,4-dione (see 13) in excellent yield.<sup>347</sup>

By similar methods 4-amino-5-ethoxycarbonylimidazoles were converted to the corresponding purines (see 19),<sup>348,349</sup> and 5-amino-4-ethoxycarbonylthiazoles were converted to the thiazolo[5,4-*d*]pyrimidinediones (see 149).<sup>349,350</sup>

Methyl as well as phenyl isocyanates were heated at 60°C for 1 hr with 2-amino-3-ethoxycarbonyl-4,5-dihydrofuran and the similarly substituted dihydrothiophene and dihydrothiopyran. The products were boiled with dilute potassium hydroxide to give good yields of 3-methyl- (and 3-phenyl-) 5,6-dihydrofuro- (and thieno-) [2,3-*d*]pyrimidine-2,4-diones (see 12) and 3-methyl-6,7-dihydrothiopyrano[2,3-*d*]pyrimidine-2,4-dione (184), respectively.<sup>327</sup>

Phenyl isothiocyanate and ethyl 2-aminotetrahydrobenzoate, when refluxed for 2 hr, gave a good yield of 3-phenyl-2-thioxo-5,6,7,8-tetrahydroquinazolin-4-one.<sup>351</sup> 2-Amino-3-ethoxycarbonyl-4,6-dimethylpyridine

<sup>345</sup> H. Rupe, *Ber. Dtsch. Chem. Ges.* 30, 1097 (1897).

<sup>346</sup> B. Taub and J. B. Hind, *J. Org. Chem.* 26, 5238 (1961).

<sup>347</sup> T. Murata, T. Sugawara, and K. Ukawa, *Chem. Pharm. Bull.* 26, 3080 (1978).

<sup>348</sup> A. H. Cook, A. C. Davis, I. Heilbron, and G. H. Thomas, *J. Chem. Soc.*, 1071 (1949); A. H. Cook and G. H. Thomas, *ibid.*, 1884 (1950).

<sup>349</sup> A. H. Cook, J. D. Downer, and I. Heilbron, *J. Chem. Soc.*, 1069 (1949).

<sup>350</sup> A. H. Cook, I. Heilbron, S. F. Macdonald, and A. P. Mahadevan, *J. Chem. Soc.*, 1064 (1949).

<sup>351</sup> G. De Stevens, A. Halamandaris, P. Wenk, R. A. Mull, and E. Schlittler, *Arch. Biochem. Biophys.* 83, 141 (1959).

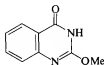


(184)

similarly furnished good yields of 3-phenyl, 3-allyl, and 3-benzyl derivatives of 2-thioxopyrido[2,3-*d*]pyrimidin-4-one.<sup>235</sup> 4-Amino-5-ethoxycarbonyl-2-benzylimidazole and methyl isothiocyanate, boiled in pyridine for 1 hr, gave 4-*N'*-methylthioureido-5-carboethoxy-2-benzylimidazole (see 18), which was cyclized by warming in 10 *N* sodium hydroxide for 1 min.<sup>348</sup>

### 6. With Cyanogen

When Finger and Zeh heated methyl anthranilate with ethyl cyanoformimidate [NC—C(NH)OEt], they obtained a product<sup>352</sup> that was later shown to be 2-ethoxyquinazolin-4-one.<sup>318</sup> The 2-methoxy analog (185) was prepared similarly.<sup>353</sup>



(185)

## IX. From Rings with an Amino Group Adjacent to a Hydrazide or a Hydroxamic Acid Group

A link with Section VIII is formed by those attempts to make an *o*-aminocarboxhydrazide that proceeded spontaneously to furnish a 3-amino annelated pyrimidine. Thus, ethyl *N*-acetylanthranilate and hydrazine hydrate, when refluxed in boiling ethanol, gave a good yield of 3-amino-2-methylquinazolin-4-one (186).<sup>354,355</sup> More often, however, the preformed hydrazide is subjected to ring closure, as in the following examples. 3-Aminopyridine-4-carboxhydrazide and triethyl orthoformate, refluxed in diethylene glycol dimethyl ether for 45 min, gave a moderate yield of

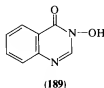
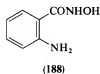
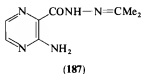
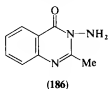
<sup>352</sup> H. Finger and W. Zeh, *J. Prakt. Chem.* [2] **81**, 466 (1910).

<sup>353</sup> R. H. McKee, *J. Prakt. Chem.* [2] **84**, 821 (1911).

<sup>354</sup> G. Heller, *J. Prakt. Chem.* [2] **111**, 36 (1925).

<sup>355</sup> J. Klosa, *J. Prakt. Chem.* [3] **31**, 140 (1966).

3-aminopyrido[3,4-*d*]pyrimidin-4-one.<sup>356</sup> 2-Acetamido-3-hydrazinocarbonylpyrazine, refluxed for 2 hr in isopropanol, formed 3-amino-2-methylpteridin-4-one (see **10**) in excellent yield.<sup>357</sup> 2-Amino-3-hydrazinocarbonylpyrazine was converted to the isopropylidene derivative (**187**) by condensation with acetone. The product was cyclized with triethyl orthoformate and acetic anhydride, and the protective group removed with 0.1 N hydrochloric acid, to furnish a good yield of 3-aminopteridin-4-one.<sup>358</sup> 2-Aminobenzoic acid hydrazide, evaporated to dryness with a mixture of acetic anhydride and water (!), gave a low yield of 3-acetamido-2-methylquinazolin-4-one.<sup>354</sup>



The use of hydroxamic acids is exemplified by the following. 2-Aminobenzhydroxamic acid (**188**), refluxed with acetic anhydride for 20 min, gave an excellent yield of 2-methyl-3-hydroxyquinazolin-4-one (**189**); 2-amino-pyridine-3-hydroxamic acid behaved similarly.<sup>359</sup> 2-Amino-3-(*N*-hydroxy-amino)carbonylpyrazine gave a good yield of 3-hydroxypteridin-4-one;<sup>360</sup> and boiling triethyl orthoformate quantitatively converted 4-amino-5-hydroxyaminocarbonylimidazole to 1-hydroxypurin-6-one (see **19**).<sup>241</sup>

## X. From Rings with an Amino Group Adjacent to an Amidine Group

The *o*-aminoamidines are excellent starting materials for preparing annelated 4-aminopyrimidines. Thus, 2-aminobenzamidine and acetone, refluxed for 15 hr in dilute hydrochloric acid, gave a moderate yield of 4-amino-2,3-dimethyl-1,2-dihydroquinazoline.<sup>276</sup> 4-Aminoimidazole-5-car-

<sup>356</sup> M. Debeljak-Šuštar, B. Stanovnik, M. Tišler, and Z. Zrimšek, *J. Org. Chem.* **43**, 393 (1978).

<sup>357</sup> F. Dallacker and G. Steiner, *Justus Liebigs Ann. Chem.* **660**, 98 (1962).

<sup>358</sup> E. C. Taylor, O. Vogl, and P. K. Loeffler, *J. Am. Chem. Soc.* **81**, 2479 (1959).

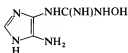
<sup>359</sup> D. Harrison and A. C. B. Smith, *J. Chem. Soc.*, 2157 (1960).

<sup>360</sup> W. B. Wright and J. M. Smith, *J. Am. Chem. Soc.* **77**, 3927 (1955).

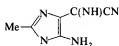
boxamidine has proved to be a versatile starting material. When refluxed with formic acid and acetic anhydride, it was changed to the 4-formamidopurine analog, which was readily cyclized to 6-aminopurine (see **19**) by refluxing in 0.5 *N* potassium hydrogen carbonate.<sup>202</sup> The same amidine, as its dihydrochloride, gave 6-amino-2-trifluoromethylpurine in good yield, when refluxed with trifluoroacetamide for 2 hr.<sup>231</sup> The same amidine and phosgene, in cold aqueous sodium hydroxide or when fused with urea, produced 6-aminopurin-2-one in moderate yield.<sup>361</sup> The same amidine, set aside at 20°C with acetic formic anhydride, quickly cyclized to 6-formamidopurine; and when various alkyl groups were incorporated in the 3-position, they appeared in the 9-position of the product without loss of yield.<sup>362</sup>

6-Amino-9-benzyl-2-methyl-8-azapurine was obtained in excellent yield by boiling 4-amino-3-benzyl-1,2,3-triazole-5-carboxamidine (see **20**) with triethyl orthoacetate and acetic anhydride for 12 hr.<sup>150</sup>

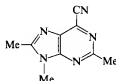
4-Amino-5-(*N*-hydroxyamidino)imidazole (**190**), refluxed for 1 hr with triethyl orthoformate and dimethylformamide, gave an excellent yield of 6-aminopurine 1-oxide. The same starting materials produced 6-amino-2-thioxopurine 1-oxide in good yield when set aside with carbon disulfide and pyridine in methanol for 5 days at 25°C.<sup>363</sup>



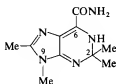
(190)



(191)



(192)



(193)

Finally, 4-amino-2,3-dimethyl-5-cyanoformimidoylimidazole (**191**), when set aside at 25°C in acetic anhydride, gave an excellent yield of 6-cyano-2,9-dimethylpurine (**192**), whereas with acetone at 25°C, scarlet crystals of 2,2,8,9-tetramethyl-1,2-dihydropurine-6-carboxamide (**193**) were obtained in excellent yield. Because **193** was the first red-colored purine to be discovered, the constitution was confirmed by X-ray crystallography.<sup>364</sup>

<sup>361</sup> L. F. Cavalieri, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.* **71**, 3973 (1949).

<sup>362</sup> K. Kadir, G. Shaw, and D. Wright, *J. C. S. Perkin I*, 2728 (1980).

<sup>363</sup> R. M. Creswell and G. B. Brown, *J. Org. Chem.* **28**, 2560 (1963).

<sup>364</sup> B. L. Booth and M. F. Proença, *J. C. S. Chem. Commun.*, 788 (1981).

## XI. From Starting Materials That Require Preliminary Rearrangement

Benzoxazines, such as "acetylanthranil" (177), are sometimes isolated as fleeting intermediates in the conversion of the *o*-disubstituted benzenes to annelated pyrimidines and hence serve to connect this section with preceding ones. The origin of acetylanthranil and its ready conversion to 2-methylquinazoline-2,4-dione have been dealt with in Section VIII,B,3. Related examples include the conversion of other types of benzoxazine to quinazolines (Sections VIII,A,6 and VIII,B,3 and of pyridooxazines to pyridopyrimidines (Section VIII,A,3), as well as of pyrazolothiazines to pyrazolopyrimidines (Sections VI,B,1 and 2).

The Hofmann, Lossen, and Curtius rearrangements will next be discussed. In the context of this chapter, the Hofmann rearrangements are those in which *o*-diamides become annelated pyrimidine-2,4-diones through spontaneous closure at the urethane stage ( $\text{—NHCO}_2\text{H}$ ). The reaction conditions usually call for potassium hypobromite (less often sodium hypochlorite solution), in which the diamide is left at  $0^\circ\text{C}$  for about 15 hr, after which it is heated at  $60^\circ\text{C}$  or  $100^\circ\text{C}$  for about 1 hr. Yields tend to be only moderate, except in a few favored cases.

The Hofmann rearrangement of phthalamide (phthalic diamide) to give quinazoline-2,4-dione was discovered in 1891, but no yields have been recorded.<sup>365</sup> *N*-Methylphthalamide gave a moderate yield of 3-methylquinazoline-2,4-dione, but 4-nitro-, 3-nitro-, and 4-chlorophthalamides produced no quinazolines.<sup>366</sup> 4,5-Bis(aminocarbonyl)imidazole (194a) furnished a moderate yield of purine-2,6-dione (xanthine) (see 19). The 1-methyl derivative (194b) gave a good yield; the principal product was 9-methylxanthine, which indicates that the amide group nearest the alkylated nitrogen atom is the more reactive.<sup>367</sup> However, a small proportion of 7-methylxanthine has been isolated from the mixture.<sup>368</sup>

Pyrazine-2,3-dicarboxamide (see 9) gave a moderate yield of pteridine-2,4-dione (see 10).<sup>369</sup> Probably the most efficient example is the rearrangement



(194a) R = H  
(194b) R = Me



(195a) R = H  
(195b) R = Me



(196)

<sup>365</sup> S. Hoogewerf and W. A. van Dorp, *Recl. Trav. Chim. Pays-Bas* **10**, 4 (1891).

<sup>366</sup> F. S. Spring and J. C. Woods, *J. Chem. Soc.*, 625 (1945).

<sup>367</sup> R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 232 (1945).

<sup>368</sup> J. Baddeley, J. G. Buchanan, and G. O. Osborn, *J. Chem. Soc.*, 3606 (1958).

<sup>369</sup> S. Gabriel and A. Sonn, *Ber. Dtsch. Chem. Ges.* **40**, 4850 (1907).

of pyridazine-4,5-dicarboxamide to pyrimidino[4,5-*d*]pyridazine-2,4-dione (see **150**). This is a potassium hypobromite reaction that gives an excellent yield.<sup>370</sup> Other Hofmann rearrangements include those of pyridine-2,3-dicarboxamide and pyridine-3,4-dicarboxamide to the corresponding pyrido-pyrimidine-2,4-diones in unstated yields.<sup>288,371</sup>

The Lossen rearrangement, like the Hofmann rearrangement, starts with a  $\text{—C(=O)N}$  to  $\text{—C=N=O}$  shift. As starting material, it requires an *o*-bishydroxamic acid, which is made to react with benzenesulfonyl chloride followed by an alkaline hydrolysis. 4,5-Bis(*N*-hydroxyaminocarbonyl)imidazole (**195a**) gave 1-hydroxypurine-2,6-dione (see **19**), and the 1-methyl derivative (**195b**) gave 1-hydroxy-7-methylpurine-2,6-dione, both in low yields. It is interesting that the position of the methyl group in the product from **195b** is so different from that of the product from **194b**.<sup>372</sup> Similarly, 2,3-bis(*N*-hydroxyamino)carbonylpyrazine gave a low yield of 3-hydroxypteridine-2,4-dione.<sup>373</sup>

The action of ammonia at 50°C on *N*-methanesulfonyloxypthalimide gave quinazoline-2,4-dione in excellent yield, presumably through the intermediate **196**, and hydroxylamine similarly furnished the 3-hydroxy derivative.<sup>374</sup> The Curtius rearrangement of *o*-bisdiazidocarbonylbenzene (phthaloyl diazide) with ammonia gave quinazoline-2,4-dione, whereas hydrazine produced the 3-amino derivative of the latter.<sup>375</sup>

The readily available isatoic anhydride (**119**) provides a useful starting material for the synthesis of annelated pyrimidines. An excellent review of the reactions of this anhydride has been published.<sup>376</sup>

When treated in water with ammonia, 2-aminobenzamide is quickly and quantitatively formed, and organic amines react similarly. These aminobenzamides can be used in all the syntheses described in Section VII.A. Conditions can be arranged so that a further reaction proceeds spontaneously, as when 5,7-dichloroisatoic anhydride gives a moderate yield of 6,8-dichloroquinazoline-2,4-dione when gently refluxed in aqueous ammonia for 1 hr.<sup>251,377</sup> Isatoic anhydride can easily be *N*-alkylated or *N*-arylated with the appropriate halide or tosylate and potassium carbonate or sodium hydride.<sup>378</sup>

<sup>370</sup> L. Di Stefano and R. N. Castle, *J. Heterocycl. Chem.* **5**, 53 (1968).

<sup>371</sup> A. C. McLean and F. S. Spring, *J. Chem. Soc.*, 2582 (1949).

<sup>372</sup> L. Bauer and D. Dhawan, *J. Heterocycl. Chem.* **2**, 220 (1965); L. Bauer, C. N. V. Nambury, and D. Dhawan, *ibid.* **1**, 275 (1964).

<sup>373</sup> L. Bauer, C. N. V. Nambury, and F. M. Hershenson, *J. Heterocycl. Chem.* **3**, 224 (1966).

<sup>374</sup> E. Kühle and R. Wegler, *Justus Liebigs Ann. Chem.* **616**, 183 (1958).

<sup>375</sup> A. Darapsky and B. Gaudian, *J. Prakt. Chem.* [2] **147**, 43 (1936).

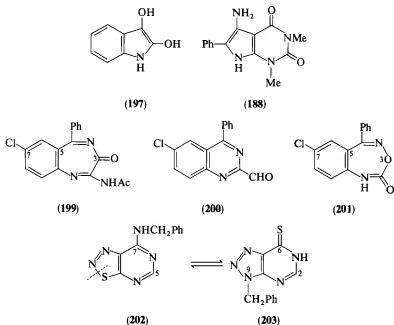
<sup>376</sup> T. Kappe and W. Stadlbauer, *Adv. Heterocycl. Chem.* **28**, 127 (1981).

<sup>377</sup> F. E. Sheibley, *J. Org. Chem.* **12**, 743 (1947); F. E. Sheibley, *ibid.* **17**, 221 (1952).

<sup>378</sup> R. W. Hall, F. C. Bernhardt, and C. F. Bean, *J. Heterocycl. Chem.* **15**, 495 (1978); G. E. Hardtman, G. Koletar, and O. R. Pfister, *ibid.* **12**, 565 (1975).

When isatoic anhydride was heated with triethyl orthoformate and aniline for 6 hr at 125°C, a good yield of quinazolin-4-one was obtained, but triethyl orthoacetate did not react.<sup>379</sup> Isatoic anhydride reacted with thioamides to give 2-substituted quinazolin-4-ones<sup>380</sup> or with benzamidine (7 hr in pyridine at 100°C) to supply a good yield of 2-phenylquinazolin-4-one.<sup>381</sup> With urea and thiourea, *N*-methylisatoic anhydride furnished 1-methylquinazolin-2,4-dione and 1-methyl-2-thioxoquinazolin-4-one.<sup>382</sup>

Some ring-expanding reactions leading to annelated pyrimidines will now be considered. The transformation of isatin-3-oxime (120) to 4-aminoquinazoline was described in Section VI,A,4. Isatin-2-oxime, when heated in dilute sodium hydroxide, rearranged to quinazoline-2,4-dione.<sup>383</sup> Isatin-3-imine in alkaline hydrogen peroxide was converted to the same substance in excellent yield.<sup>384</sup>



2,3-Dihydroxyindole (197) expands to 3-hydroxyquinazoline-2,4-dione in excellent yield when set aside in aqueous methanol with amyl nitrite and

<sup>379</sup> R. H. Clark and E. C. Wagner, *J. Org. Chem.* **9**, 55 (1944)..

<sup>380</sup> E. Ziegler, W. Steiger, and T. Kappe, *Monatsh. Chem.* **100**, 150, 948 (1969).

<sup>381</sup> K. Nagahara, K. Takagi, and T. Ueda, *Chem. Pharm. Bull.* **24**, 1197 (1976).

<sup>382</sup> W. Steiger, T. Kappe, and E. Ziegler, *Monatsh. Chem.* **100**, 528 (1969).

<sup>383</sup> G. Heller, *Ber. Dtsch. Chem. Ges.* **49**, 2757 (1916).

<sup>384</sup> G. Jacini, *Gazz. Chim. Ital.* **73**, 85 (1943).

sodium carbonate.<sup>385</sup> As an example of expansion through oxidation, 5-amino-1,3-dimethyl-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4-dione (**198**) was converted to 1,3-dimethyl-7-phenylpyrimidino[4,5-*d*]pyrimidine-2,4,5-trione (see 7) by heating with lead tetraacetate at 65°C for 3 hr.<sup>386</sup>

Ring-contracting reactions can lead to annelated pyrimidines. For example, 2-acetamido-7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-3-one (**199**) was converted by refluxing ethanolic hydrochloric acid to 6-chloro-2-ethoxycarbonyl-4-phenylquinazoline.<sup>387</sup> The closely related alcohol, 7-chloro-3-hydroxy-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine, gave 6-chloro-4-phenylquinazolin-2-aldehyde (**200**) when left in dilute acid at 25°C.<sup>388</sup> At its melting point, 7-chloro-5-phenyl-3,1,4-benzoxadiazepin-2-one (**201**) changed to 6-chloro-3-phenylquinazoline-2,4-dione, apparently through a Beckmann arrangement.<sup>389</sup>

We shall conclude with a few words about the Christmas rearrangement, discovered by this author during one of the heat waves common in Australia at that time of the year. 7-Benzylamino-1,2,3-thiadiazolo[5,4-*d*]pyrimidine (**202**), into which 9-benzyl-8-azapurine-6-thione (**203**) spontaneously changed, was quantitatively converted back to the thermostable sodium salt of the latter by boiling in 1 *N* sodium hydroxide for 30 min. The 7-amino and 7-methylamino analogs rearranged similarly.<sup>224</sup> The dashed line in **202** indicates where the ring opens to give the diazo group that attacks the 7-amino group. 7-Amino-1,2,3-thiadiazolo[5,4-*d*]pyrimidine-5-thione was similarly changed to the stable sodium salt of 8-azapurine-2,6-dithione.<sup>179</sup>

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<sup>385</sup> G. Jacini, *Gazz. Chim. Ital.* **74**, 3 (1944).

<sup>386</sup> F. Yoneda and M. Higuchi, *J. C. S. Chem. Commun.*, 402 (1972).

<sup>387</sup> S. C. Bell, C. Gochman, and S. J. Childress, *J. Org. Chem.* **28**, 3010 (1963).

<sup>388</sup> L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *J. Org. Chem.* **29**, 332 (1964).

<sup>389</sup> T. S. Sulkowski and S. J. Childress, *J. Org. Chem.* **27**, 4424 (1962).



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*gem*-Dithienylalkanes and Their Derivatives

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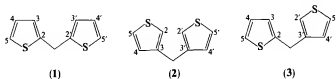
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**I. Introduction**

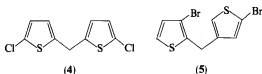
The main interest in *gem*-dithienylalkane derivatives in recent years has been in their use as synthetic intermediates, via reductive desulfurization, for a variety of aliphatic substances (notably carboxylic acids) and as sub-

stances of potential pharmacological value. The compounds have a long history, but their chemistry has not been previously reviewed in any detail.

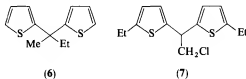
There are three possible isomeric dithienylmethanes; the 2,2'-isomer (1) has been known<sup>1</sup> for almost 100 years, but the 3,3'- (2) and 2,3'-dithienylmethanes (3) were not prepared until 1968<sup>2</sup> and 1964,<sup>3</sup> respectively.



There seems to be no universally accepted nomenclature for these compounds and their derivatives. For example, 1 has been called di- $\alpha$ -thienylmethane, di-2-thienylmethane, 2,2'-dithienylmethane, and 2,2'-methyleneedithiophene. The dichloro compound 4 has been described as bis(5-chloro-2-thienyl)methane and as 2,2'-methylenebis-5-chlorothiophene. In yet another notation system the dithienylmethane is considered to be the basic system present, and other groups are described as substituents of it; thus, 4 becomes 5,5'-dichloro-2,2'-dithienylmethane, and 5 is 3,5'-dibromo-2,3'-dithienylmethane. Although this last system is not entirely free of difficulties, it appears to the author to be the least clumsy of the various alternatives and is used wherever possible throughout this chapter.



The nomenclature for *gem*-dithienylalkanes is reasonably straightforward, the thiophene rings being described as substituents of the parent alkane. Compound 6 is thus 2,2-bis(2-thienyl)butane, and 7 is 1-chloro-2,2-bis-(5-ethyl-2-thienyl)ethane.



<sup>1</sup> A. Peter, *Chem. Ber.* **17**, 1341 (1884).

<sup>2</sup> A. Kraak, A. K. Wiersma, P. Jordens, and H. Wynberg, *Tetrahedron* **24**, 3381 (1968).

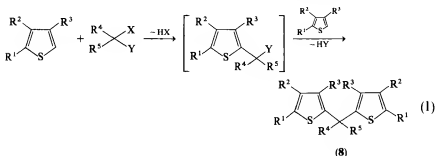
<sup>3</sup> H. Wynberg and A. Kraak, *J. Org. Chem.* **29**, 2455 (1964).

Dithienylalkanes occur in certain shale oils of high sulfur content. The compounds described<sup>4,5</sup> are bis(5-methyl-2-thienyl)ethanes and -propanes, both with and without additional methyl groups in the thiophene rings; 5,5'-dialkyl-2,2'-dithienylmethanes are also present. A patent<sup>6</sup> refers to the use of 1,1-bis(2-thienyl)ethane, 2,2-bis(2-thienyl)propane, and 2-hydroxyphenylbis(2-thienyl)methane as antioxidants for mineral oils, but otherwise there seems to be no commercial use for simple dithienylalkanes.

## II. Synthesis

### A. INTRODUCTION

There are two principal approaches to the synthesis of *gem*-dithienylalkanes. In the first, two molecules of a thiophene are united through a single carbon atom provided by a second component. This kind of synthesis gives rise to products (8) in which the two thiophene rings are symmetrically substituted and includes reactions that involve electrophilic substitution of each of the thiophene rings by species arising from the second component

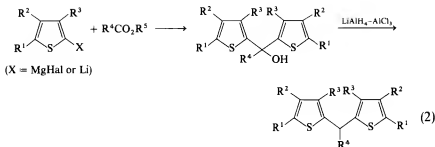


(Eq. 1). In this way aldehydes ( $R^5 = H$ ;  $XY = O$ ), ketones ( $R^4, R^5 = \text{alkyl}$ , etc;  $XY = O$ ),  $\alpha$ -halogenoalkyl ethers ( $X = \text{halogen}$ ;  $Y = O\text{-alkyl}$ ), acetals and ketals ( $X = Y = O\text{-alkyl}$ ), and *gem*-dihalogeno compounds ( $X = Y = \text{halogen}$ ) can be employed. Alternatively, a thienyl Grignard reagent or thienyllithium may be reacted with a carboxylic acid derivative (normally an ester) to produce an  $\alpha,\alpha$ -dithienylalkanol, which can be reduced to the dithienylalkane (Eq. 2). Although the great majority of preparations of this type have been concerned with the formation of bis(2-thienyl)alkanes, they can also be used to obtain 3,3' (but not 2,2') compounds.

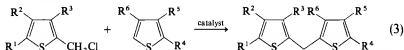
<sup>4</sup> M. Pailer and H. Grunhaus, *Monatsh. Chem.* **104**, 312 (1973).

<sup>5</sup> M. Pailer and L. Berner-Fenz, *Monatsh. Chem.* **104**, 339 (1973).

<sup>6</sup> Ger. Offen. 938,740 [*CA* **53**, 7578 (1959)].



In the second class of synthesis two thiophene rings become joined through a carbon atom that is already a substituent of one of them; by this means symmetrically and unsymmetrically substituted products in the 2,2', 2,3', and 3,3' series are available. Three main reaction types have been employed in this approach. In one of these a thiophene is alkylated with a thenyl halide (Eq. 3). Friedel-Crafts acylation of a thiophene by a thenoyl chloride or thenoic acid followed by reduction of the resulting dithienyl ketone provides a second route in this category. The last and most versatile synthesis in this class involves reaction of a thienyllithium (or Grignard reagent) with a thienylaldehyde or thienyl ketone; reduction of the carbinol (see Eq. 2) then gives the dithienylalkane.



A more detailed survey of these reactions will now be given; the section concludes with an account of some other, less general reactions that have led to dithienylalkanes.

## B. CONDENSATION OF AN ALDEHYDE OR KETONE WITH A THIOPHENE

The simplest possible case involves formaldehyde and thiophene, and 2,2'-dithienylmethane is formed as a by-product in the chloromethylation of thiophene with formaldehyde-hydrochloric acid<sup>7,8</sup>; replacement of the hydrochloric acid by hydrofluoric acid causes the dithienylmethane to become the major product (52%).<sup>9</sup> Under the normal chloromethylation conditions 2-methylthiophene gave only a minor amount (4%) of 2-chloro-

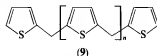
<sup>7</sup> F. F. Blicke and J. H. Burckhalter, *J. Am. Chem. Soc.* **64**, 477 (1942).

<sup>8</sup> T. Ivanov and D. Mondeshka, *J. Prakt. Chem.* [2] **315**, 993 (1973).

<sup>9</sup> T. L. Cairns, B. C. McKusick, and V. Weinmayr, *J. Am. Chem. Soc.* **73**, 1270 (1951).

methyl-5-methylthiophene and a very good yield (64%) of 5,5'-dimethyl-2,2'-dithienylmethane.<sup>10</sup> Related to these reactions are those reported by Hartough *et al.*,<sup>11-13</sup> who found that 5,5'-dimethyl-2,2'-dithienylmethane was produced in significant amounts (~45%), together with 5-methyl-2-thenylamine, when 2-methylthiophene was reacted with formaldehyde and either ammonium chloride or dimethylamine hydrochloride. Thiophene itself gave mainly polymer under the same conditions.

In the presence of a catalyst (zinc chloride) the combination thiophene-formaldehyde-hydrochloric acid leads to 2,2'-dithienylmethane as the major product (50-65%); higher condensation products (**9**,  $n = 1, 2$ , etc.) are also formed, in lower yields. When the reaction with formaldehyde is applied to



2-substituted thiophenes, the possibility of polymerization via a free  $\alpha$ -position is removed and, provided that the substituent is not too deactivating, good yields of 5,5'-disubstituted 2,2'-dithienylmethanes can be expected, e.g., from 2-methylthiophene [(ZnCl<sub>2</sub>) 65%,<sup>14</sup> (HF) 72%<sup>9</sup>] and from 2-chlorothiophene [(ZnCl<sub>2</sub>) 51%,<sup>15</sup> (HF) 54%<sup>9</sup>]. The reasonable results from 2-chlorothiophene contrast with those from 2-bromothiophene; this may reflect the stability of the final product rather than the efficiency of the condensation, since 5,5'-dibromo-2,2'-dithienylmethane decomposes rather readily.<sup>16</sup> Thiophenes carrying electron-withdrawing substituents at C-2 condense poorly, or not at all, e.g., 2-nitrothiophene (24%),<sup>17</sup> 2-acetylthiophene ("low yield"),<sup>9</sup> and ethyl 2-thenoate (no reaction).<sup>18</sup>

There is some confusion about the chloromethylation of 2,5-dimethylthiophene with formaldehyde-hydrochloric acid. Buu-Hoi and Hoan<sup>19</sup> reported that 2,2',5,5'-tetramethyl-3,3'-dithienylmethane was the major product, but others<sup>20</sup> found that only chloromethylated thiophenes were produced. In

<sup>10</sup> W. S. Emerson and T. M. Patrick, *J. Org. Chem.*, **14**, 790 (1949).

<sup>11</sup> H. D. Hartough, S. J. Lukasiewicz, and E. H. Murray, *J. Am. Chem. Soc.*, **70**, 1146 (1948).

<sup>12</sup> H. D. Hartough, U.S. Patent 2,577,191 (1951) [CA 46, 9609 (1952)].

<sup>13</sup> H. D. Hartough and S. J. Lukasiewicz, U.S. Patent 2,559,567 (1951) [CA 46, 1048 (1952)].

<sup>14</sup> Y. L. Goldfarb and Y. L. Danyushevsky, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, 1395 (1956).

<sup>15</sup> M. Ahmed, J. Ashby, M. Ayad, and O. Meth-Cohn, *J. C. S. Perkin I*, 1099 (1973).

<sup>16</sup> Y. L. Goldfarb and M. L. Kirmalova, *J. Gen. Chem. USSR (Engl. Transl.)*, **26**, 3797 (1956).

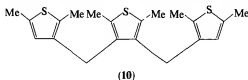
<sup>17</sup> Y. Inaba, G. Kimura, S. Umiji, and M. Kinoene, Japanese Patent 9986 (1962) [CA 59, 9988 (1963)].

<sup>18</sup> J. M. Barker and R. Smith, unpublished work.

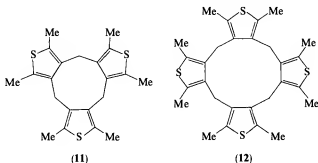
<sup>19</sup> N. P. Buu-Hoi and N. Hoan, *Recl. Trav. Chim. Pays-Bas*, **68**, 5 (1949).

<sup>20</sup> T. S. Cantrell and B. L. Harrison, *Tetrahedron Lett.*, 477 (1967)

the presence of zinc chloride, however, 2,5-dimethyl-<sup>21,22</sup> and 2,5-diethylthiophene<sup>23</sup> give modest yields of the diarylmethane. In the former case it was reported that substantial amounts of the linear tris condensation product **10** were also formed. Meth-Cohn<sup>22</sup> found that a small quantity of the cyclic



trimer **11** was also present and, by suitable variation of reaction conditions, was able to prepare this interesting substance in reasonable yield; it was accompanied by a little of the corresponding tetramer **12**. The main agents



that have been employed to bring about the condensation of thiophenes with aldehydes other than formaldehyde are phosphorus pentoxide-chloroform, 72% sulfuric acid, or sulfuric acid-acetic acid. A great variety of aldehydes have been used; in particular, numerous dithienylalkanes have been prepared from chlorinated aldehydes in attempts to obtain substances with DDT-like activity. Such preparations are successful not only with thiophene itself, but also with alkylthiophenes and with some deactivated thiophenes (including 2,5-dichloro-<sup>24</sup> and 2,3,4-trichlorothiophene<sup>25</sup>). On the other hand, 2-octyl, 2-benzoyl-, 2,5-di-*tert*-butyl-, and 2,3,5-trichlorothiophene all failed to react with chloral.<sup>24</sup> Almost invariably 72% sulfuric acid has been used to condense thiophenes with ketones; the reactions show no unexpected features.

<sup>21</sup> Y. L. Goldfarb and M. S. Kondakova, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* 487 (1956).

<sup>22</sup> O. Meth-Cohn, *Tetrahedron Lett.*, 91 (1973).

<sup>23</sup> Y. L. Goldfarb and Y. B. Volkenshtein, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 737 (1963) [*CA* 59, 7459 (1963)].

<sup>24</sup> J. F. Feeman, J. R. Dove, and E. D. Amstutz, *J. Am. Chem. Soc.* **70**, 3136 (1948).

<sup>25</sup> R. H. Sieber and P. Hornig, *Justus Liebigs Ann. Chem.* **743**, 144 (1971).

TABLE I  
PRODUCTS (13 AND 14) FROM CONDENSATIONS OF THIOPHENE WITH  
ALDEHYDES OR KETONES

R <sup>1</sup>	R <sup>2</sup>	Agent <sup>a</sup>	Yield (%)		Ref.
			13	14	
H	H	a	65		26
H	H	a	50	11	14
H	H	b	52		9
H	CCl <sub>3</sub>	c	73		24
H	CCl <sub>3</sub>	d	58		27
H	CCl <sub>3</sub>	d	30		1
H	CBr <sub>3</sub>	d	30		1
H	CH <sub>3</sub>	b	39		9
H	C <sub>2</sub> H <sub>5</sub>	e	6		28
H	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	e	7		28
H	C <sub>6</sub> H <sub>5</sub>	f	26		29
H	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	e	35		30
H	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	f	46		29
H	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	f	56		29
H	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	e	58		31
H	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	f	48		29
H	2-Thienyl	e	14		28
CH <sub>3</sub>	CH <sub>3</sub>	c	50		32
CH <sub>3</sub>	CH <sub>3</sub>	c	57		33
CH <sub>3</sub>	CH <sub>3</sub>	c	47		34
CH <sub>3</sub>	CH <sub>3</sub>	c	50	15	35-37
CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	c	66	8	38
CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	c	48	17	36, 37
C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	c	48	17	37
C <sub>2</sub> H <sub>5</sub>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	c	52		39
<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	c	47	16	37
<i>n</i> -C <sub>4</sub> H <sub>9</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	c	44	15	37
CH <sub>3</sub>	2-Thienyl	c	54		38
CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	c	49		38
1,1-Cyclohexyl		c	39		36
CH <sub>3</sub>	CH <sub>3</sub> CO	e	35		37
CH <sub>3</sub>	CH <sub>2</sub> Cl	c	61		40
CH <sub>3</sub>	CO <sub>2</sub> H	c	45		40
CH <sub>2</sub> Cl	CH <sub>2</sub> Cl	c	45		25

<sup>a</sup> Key: a, HCl-ZnCl<sub>2</sub>; b, HF; c, 72% H<sub>2</sub>SO<sub>4</sub>; d, H<sub>2</sub>SO<sub>4</sub>-CH<sub>3</sub>CO<sub>2</sub>H; e, P<sub>2</sub>O<sub>5</sub>-CHCl<sub>3</sub>; f, c H<sub>2</sub>SO<sub>4</sub>.



TABLE II  
PRODUCTS (8) FROM CONDENSATION OF SUBSTITUTED THIOPHENES WITH  
ALDEHYDES OR KETONES

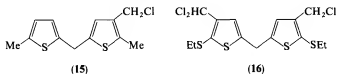
R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Agent <sup>a</sup>	Yield (%)	Ref.
CH <sub>3</sub>	H	H	H	H	a	65	14
CH <sub>3</sub>	H	H	H	H	b	72	9
CH <sub>3</sub>	H	H	H	H	g	64	10
CH <sub>3</sub>	H	H	H	H	h	41	11-13
CH <sub>3</sub>	H	H	H	H	i	45	11
CH <sub>3</sub>	H	H	H	CCl <sub>3</sub>	d	75	41
CH <sub>3</sub>	H	H	H	CCl <sub>3</sub>	d	43	27
CH <sub>3</sub>	H	H	H	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	e	66	30
CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	c	79	38
CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	c	87	36
CH <sub>3</sub>	H	H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	c	62	36
C <sub>2</sub> H <sub>5</sub>	H	H	H	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	e	34	30
<i>i</i> -C <sub>4</sub> H <sub>9</sub>	H	H	H	CCl <sub>3</sub>	c	14	24
<i>i</i> -C <sub>4</sub> H <sub>9</sub>	H	H	H	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	e	58	30
H	H	CH <sub>3</sub>	H	H	b	89	9
H	H	CH <sub>3</sub>	H	CCl <sub>3</sub>	d	30	27
Cl	H	H	H	H	b	54	9
Cl	H	H	H	H	a	51	15
Cl	H	H	H	CCl <sub>3</sub>	c	62	24
Cl	H	H	H	CCl <sub>3</sub>	d	32	27
Cl	H	H	CH <sub>3</sub>	CH <sub>3</sub>	c	61	38
Br	H	H	H	H	a	21	16
Br	H	H	H	CCl <sub>3</sub>	c	35	24
Br	H	H	H	CCl <sub>3</sub>	d	57	27
I	H	H	H	CCl <sub>3</sub>	d	—	42
I	H	H	H	C <sub>6</sub> H <sub>5</sub>	e	22	28
NO <sub>2</sub>	H	H	H	H	d	24	17
CH <sub>2</sub> CH <sub>2</sub> OH	H	H	H	H	c	"low"	43
SCH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	c	68	44
SCH <sub>3</sub>	H	H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	c	72	44
SC <sub>2</sub> H <sub>5</sub>	H	H	H	H	c	59	44
SC <sub>2</sub> H <sub>5</sub>	H	H	H	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	c	61	44
SC <sub>2</sub> H <sub>5</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	c	87	44
SC <sub>2</sub> H <sub>5</sub>	H	H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	c	83	44
NMNO <sup>b</sup>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	g	34	45
NMNO <sup>b</sup>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	g	45	45
NMNO <sup>b</sup>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	4-BrC <sub>6</sub> H <sub>4</sub>	g	43	45
H	Cl	Cl	H	CCl <sub>3</sub>	c	73	25
Cl	Cl	Cl	H	CCl <sub>3</sub>	c	96	25
CH <sub>3</sub>	CO <sub>2</sub> Et	OH	H	H	g	—	46
CH <sub>3</sub>	CO <sub>2</sub> Et	OH	H	C <sub>6</sub> H <sub>5</sub>	g	—	46

<sup>a</sup> Key: a, HCl-ZnCl<sub>2</sub>; b, HF; c, 72% H<sub>2</sub>SO<sub>4</sub>; d, H<sub>2</sub>SO<sub>4</sub>-CH<sub>3</sub>CO<sub>2</sub>H; e, P<sub>2</sub>O<sub>5</sub>-CHCl<sub>3</sub>; g, HCl; h, NH<sub>4</sub>Cl; i, (CH<sub>3</sub>)<sub>2</sub>NH·HCl.

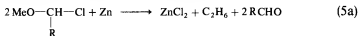
<sup>b</sup> *N*-Morpholino.



The conflicting reports of the results of the chloromethylation of 2,5-dimethylthiophene with formaldehyde–hydrochloric acid have already been mentioned. With bischloromethyl ether in acetic acid this substance gives a mixture of 3-chloromethyl-2,5-dimethylthiophene (46%), 3,4-bis(chloromethyl)-2,5-dimethylthiophene (12%), and 4-chloromethyl-5,5'-dimethyl-2,2'-dithienylmethane (**15**)<sup>49</sup> (19%). 2,5-Diethylthiophene, on the other hand, yields only a very small quantity of a dithienylmethane under these conditions. The formation of a chloromethylated dithienylmethane was also observed in the bischloromethyl ether treatment of 2-ethylthiophene.<sup>50</sup> The product, **16**, was not actually isolated, but its presence was demonstrated by further reactions (see Section III,D); the yields in these reactions imply that **16** was a rather minor component in the crude reaction mixture.



In the presence of a suitable catalyst the dithienylalkane becomes the major product in these reactions with chloroalkyl ethers. The catalysts employed have included tin(IV) chloride,<sup>51</sup> aluminum chloride,<sup>23</sup> concentrated sulfuric acid,<sup>25</sup> and zinc dust.<sup>52,53</sup> It is suggested in the last case that the zinc and chloroalkyl ether react to produce the aldehyde and zinc chloride (Eq. 5a). However, it seems more likely that some zinc chloride would be produced in a coupling reaction (Eq. 5b) and would then catalyze the condensation of thiophene and the chloroalkyl ether in the usual way. With a sufficiently vigorous catalyst even deactivated



thiophenes can be induced to react; the formation (77% yield) of bis(5-acetyl-2-ethyl-3-thienyl) methane (**17**) serves as an illustration (Eq. 6).<sup>23</sup>

<sup>49</sup> P. Cagniant, G. Merle, and D. Cagniant, *Bull. Soc. Chim. Fr.*, 302 (1970).

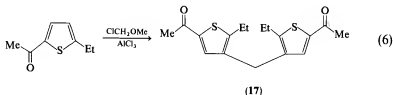
<sup>50</sup> Y. L. Goldfarb, M. A. Kalik, and M. L. Kirmalova, *Khim. Geterotsikl. Soedin.*, 483 (1969) [*CA* 72 21550 (1970)].

<sup>51</sup> H. Gross and J. Freiberg, *J. Prakt. Chem.* [2] 312, 284 (1970).

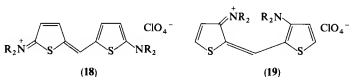
<sup>52</sup> I. I. Lapkin and L. D. Orlova, *Uch. Zap.—Pensk. Gos. Univ. im. A. M. Gor'kogo* 159, 281 (1966) [*CA* 69, 59016 (1968)].

<sup>53</sup> I. I. Lapkin and L. D. Orlova, *Khim. Geterotsikl. Soedin.*, 1181 (1970) [*CA* 74, 87726 (1971)].

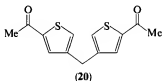
Acetals and ketals can replace chloroalkyl ethers in these condensations; indeed, the first synthesis<sup>1</sup> of 2,2'-dithienylmethane involved methylal and



thiophene. A particularly interesting example uses ethyl orthoformate and perchloric acid to couple 2- and 3-dialkylaminothiophenes.<sup>54</sup> Very high yields of cationic species **18** and **19** are obtained; it seems likely that extensive delocalization of the positive charge prevents reaction with a third thiophene molecule.



Finally, mention should be made of the union of two thiophene rings through a single carbon atom derived from *gem*-polychloroalkyl compounds. Nahke<sup>55</sup> described the preparation of phenyldi-2-thienylmethane from thiophene and benzotrichloride–aluminum chloride, and Russian workers<sup>56</sup> reported the formation of **20**, in low yield, from 2-acetylthiophene and dichloromethane–aluminum chloride.



A survey of syntheses of 2,2'-dithienylmethanes and bis(2-thienyl)alkanes that have utilized  $\alpha$ -chloroalkyl ethers or acetals is presented in Table III (Eq. 1, [X = Cl, Y = OR or X = Y = OR]). There have been very few applications of this route to bis(3-thienyl)-alkanes.

<sup>54</sup> H. Hartmann and S. Sheithauer, *J. Prakt. Chem.* [2] **311**, 827 (1969).

<sup>55</sup> A. Nahke, *Chem. Ber.* **30**, 2041 (1897).

<sup>56</sup> A. P. Yakubov, Y. K. Sudarushkin, L. I. Belenkii, and Y. L. Goldfarb, *Zh. Org. Kim.* **9**, 1521 (1973) [*CA* **79**, 91864 (1973)].

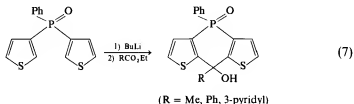
TABLE III  
PRODUCTS (8) FROM CONDENSATION OF THIOPHENES WITH  $\alpha$ -CHLOROALKYL  
ETHERS OR ACETALS

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	X	Y	Agent <sup>a</sup>	Yield (%)	Ref.
H	H	H	H	H	Cl	OMe	a	30	52
H	H	H	H	CH <sub>3</sub>	Cl	OMe	a	32	52
H	H	H	H	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	Cl	OMe	a	30	53
H	H	H	H	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Cl	OMe	a	36	53
H	H	H	H	CH <sub>2</sub> Cl	OE <sub>t</sub>	OE <sub>t</sub>	b	60	25
H	H	H	H	CH <sub>2</sub> Cl	OE <sub>t</sub>	OE <sub>t</sub>	c	27	55
H	H	H	H	CH <sub>2</sub> Br	OE <sub>t</sub>	OE <sub>t</sub>	c	7	55
H	H	H	H	CHCl <sub>2</sub>	OE <sub>t</sub>	OE <sub>t</sub>	c	36	55
H	H	H	H	CHCl <sub>2</sub>	OE <sub>t</sub>	OE <sub>t</sub>	d	67	25
H	H	H	H	CH <sub>3</sub> CHCl	OE <sub>t</sub>	OE <sub>t</sub>	d	58	25
H	H	H	H	CCl <sub>3</sub>	OE <sub>t</sub>	OE <sub>t</sub>	d	69	25
H	H	H	H	CH <sub>3</sub> CHCl-CHCl	OE <sub>t</sub>	OE <sub>t</sub>	d	56	25
H	H	H	H	CH <sub>3</sub> CHCl-CCl <sub>2</sub>	OE <sub>t</sub>	OE <sub>t</sub>	d	74	25
H	H	H	CH <sub>3</sub>	CH <sub>2</sub> Cl	OE <sub>t</sub>	OE <sub>t</sub>	b	65	25
H	H	H	CH <sub>3</sub>	CH <sub>3</sub> CHCl	OE <sub>t</sub>	OE <sub>t</sub>	d	50	25
H	H	H	H	CO <sub>2</sub> CH <sub>3</sub>	Cl	OMe	e	34	51
CH <sub>3</sub>	H	H	H	H	Cl	OMe	a	47	52
CH <sub>3</sub>	H	H	H	CH <sub>3</sub>	Cl	OMe	a	37	52
CH <sub>3</sub>	H	H	H	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Cl	OMe	a	61	53
CH <sub>3</sub>	H	H	H	CH <sub>2</sub> Cl	OE <sub>t</sub>	OE <sub>t</sub>	b	84	25
C <sub>2</sub> H <sub>5</sub>	H	H	H	H	Cl	OMe	f	57	48
C <sub>2</sub> H <sub>5</sub>	H	H	H	H	Cl	OMe	a	44	52
C <sub>2</sub> H <sub>5</sub>	H	H	H	CH <sub>3</sub>	Cl	OMe	a	32	52
C <sub>2</sub> H <sub>5</sub>	H	H	H	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	Cl	OMe	a	61	53
C <sub>2</sub> H <sub>5</sub>	H	H	H	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Cl	OMe	a	50	53
C <sub>2</sub> H <sub>5</sub>	H	H	H	CH <sub>2</sub> Cl	OE <sub>t</sub>	OE <sub>t</sub>	b	79	25
<i>n</i> -C <sub>3</sub> H <sub>7</sub>	H	H	H	H	Cl	OMe	a	53	52
<i>n</i> -C <sub>3</sub> H <sub>7</sub>	H	H	H	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Cl	OMe	a	50	53
Cl	H	H	H	H	Cl	OMe	a	38	52
Cl	H	H	H	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Cl	OMe	a	16	53
Cl	H	H	H	CH <sub>2</sub> Cl	OE <sub>t</sub>	OE <sub>t</sub>	b	49	25
Br	H	H	H	H	Cl	OMe	a	36	52
Br	H	H	H	CH <sub>3</sub>	Cl	OMe	a	32	52
Br	H	H	H	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	Cl	OMe	a	34	53
Br	H	H	H	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Cl	OMe	a	30	53
I	H	H	H	H	Cl	OMe	a	30	52
H	Cl	Cl	H	CH <sub>2</sub> Cl	Cl	OE <sub>t</sub>	g	72	25
Cl	Cl	Cl	H	CH <sub>2</sub> Cl	Cl	OE <sub>t</sub>	g	77	25

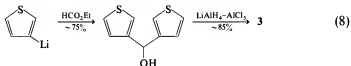
<sup>a</sup> Key: a, Zn dust; b, 72% H<sub>2</sub>SO<sub>4</sub>; c, P<sub>2</sub>O<sub>5</sub>-CHCl<sub>3</sub>; d, H<sub>2</sub>SO<sub>4</sub>-CH<sub>3</sub>CO<sub>2</sub>H; e, SnCl<sub>4</sub>; f, CH<sub>3</sub>CO<sub>2</sub>H; g, c H<sub>2</sub>SO<sub>4</sub>.

#### D. REACTION OF A THIENYLMAGNESIUM HALIDE OR THIENYLITHIUM WITH AN ESTER

The normal reaction of an organolithium or Grignard reagent with an ester, to give a tertiary alcohol, is observed with both the 2- and the 3-thienyl organometallic compounds. The resulting dithienylcarbinols, and the alkenes obtained when they are dehydrated, are likely to possess pharmacological activity. Many such compounds have been prepared for testing, and an account is given in Section IV. The condensation is successful with a wide range of esters; the presence in the ester of  $-\text{OH}$ ,<sup>57</sup>  $-\text{CONHNHR}$ ,<sup>58</sup>  $-\text{CONHNR}^1\text{R}^2$ ,<sup>59</sup> or  $-\text{CO}-\text{NH}-\text{N}=\text{CH}-\text{C}_6\text{H}_5$ ,<sup>60</sup> apparently has no adverse effect. Particularly interesting reactions by Lampin and Mathey<sup>61</sup> produced dithienylmethanol derivatives from triarylphosphines and their oxides (e.g., Eq. 7).



In certain cases the carbinols have been reduced to the corresponding dithienylalkane—for example, 3,3'-dithienylmethane (3, Eq. 8).<sup>2,15</sup> The preferred agent for such reductions is lithium aluminum hydride–aluminum chloride–ether,<sup>62</sup> but tin(II) chloride–hydrochloric acid seems to be equally effective.<sup>63</sup> Provided that substituents can withstand the reduction process, this synthetic approach to dithienylalkanes is obviously a very versatile one.



<sup>57</sup> I. I. Lapkin, R. M. Kislovets, and T. Y. Subocheva, *Zh. Org. Khim.* **5**, 881 (1969) [*CA* **1**, 38248 (1969)].

<sup>58</sup> I. S. Berdinskii and E. Y. Posyagina, *Uch. Zap.—Permsk. Gos. Univ. im. A. M. Gor'kogo* **229**, 262 (1970) [*CA* **77**, 113273 (1972)].

<sup>59</sup> I. S. Berdinskii and E. Y. Posyagina, *Zh. Org. Khim.* **6**, 2214 (1970) [*CA* **74**, 41855 (1971)].

<sup>60</sup> I. S. Berdinskii, L. V. Kazakova, G. P. Petyunin, P. A. Petyunin, and V. P. Baboshko, *Zh. Org. Khim.* **10**, 2077 (1974) [*CA* **82**, 72688 (1975)].

<sup>61</sup> J. P. Lampin and F. Mathey, *J. Organomet. Chem.* **71**, 239 (1974).

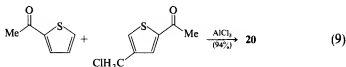
<sup>62</sup> J. Blackwell and W. J. Hickinbottom, *J. Chem. Soc.*, 1405 (1961).

<sup>63</sup> F. Leonard and I. Ehranthal, *J. Am. Chem. Soc.* **73**, 2216 (1951).

### E. ALKYLATION OF A THIOPHENE WITH A THENYL CHLORIDE

It seems likely that the formation of dithienylmethanes from a thiophene, formaldehyde, hydrochloric acid, and zinc chloride involves the intermediacy of the thenyl chloride. A modification of the synthesis uses a preformed thenyl chloride, which has the advantage that unsymmetric dithienylmethanes can also be prepared. 2,2'-Dithienylmethane has been made in excellent yield (92%) in this way using zinc chloride as catalyst<sup>64</sup>; antimony trichloride has been used with less success (67%).<sup>65</sup> Tin(IV) chloride is generally a satisfactory catalyst for Friedel-Crafts reactions of thiophenes, and it is the common catalyst for thenylation of thiophenes. The normal directive influences of substituents are observed; for example, 3-bromothiophene is thenylated at C-2 by 2-chloromethylthiophene to give 3-bromo-2,2'-dithienylmethane<sup>66,67</sup> in rather poor yield. One might expect that steric effects would make the situation worse if 3-bromothiophene were reacted with 3-bromo-2-chloromethylthiophene, but in practice the yield was better in the latter case (48% as opposed to 29%).<sup>2</sup>

Electrophilic substitution of a thiophene ring bearing an electron-withdrawing substituent at C-2 generally requires a powerful catalyst and gives a mixture of the 2,4- and 2,5-disubstituted isomers, the former predominating. This preference was particularly marked in the aluminum chloride-catalyzed alkylation of 2-acetylthiophene with 2-acetyl-4-chloromethylthiophene, which led to an excellent yield of the 3,3'-dithienylmethane **20** (Eq. 9).<sup>68</sup> The corresponding reaction between 2-acetylthiophene and 2-acetyl-5-chloromethylthiophene was considerably less successful.<sup>68</sup> Aluminum chloride was overefficient in catalyzing the condensation of 2,5-dimethylthiophene and 2,5-dimethyl-3-chloromethylthiophene; the dithienylmethane was accompanied by the further substitution product **10**.<sup>21</sup>



<sup>64</sup> Y. Inaba, M. Kinoene, and G. Kimura, Japanese Patent 9321 (1962) [*CA* **59**, 12763 (1963)].

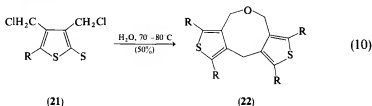
<sup>65</sup> Y. Inaba, G. Kimura, and M. Kinoene, Japanese Patent 9230 (1962) [*CA* **59**, 11428 (1963)].

<sup>66</sup> D. H. MacDowell and J. C. Wisowaty, *J. Org. Chem.* **36**, 4004 (1971).

<sup>67</sup> H. Wynberg, J. de Witt, and H. J. M. Sinnige, *J. Org. Chem.* **35**, 711 (1970).

<sup>68</sup> L. I. Belenkii, I. B. Karmanova, and Y. L. Goldfarb, *Zh. Org. Khim.* **9**, 1514 (1973) [*CA* **79**, 105021 (1973)].

An electrophilic substitution step must be involved in the formation of the tricyclic substance **22** ( $R = \text{Me}$ ) (Eq. 10); the reaction failed when  $R$  was ethyl or *tert*-butyl (**21**).<sup>69</sup>



Nucleophilic substitution of chloride ion from a thenyl chloride by a suitable thienyl species (e.g., a thienyllithium) can also lead to a dithienylmethane, but this approach has been little used. It was successful for the preparation of 2,2'-dithienylmethane itself,<sup>70</sup> but in the interaction of 3-bromo-2-chloromethylthiophene and 3-bromo-2-thienyllithium the yield was low (16%)<sup>3</sup> and compared unfavorably with that in the Friedel-Crafts reaction.<sup>2</sup>

## F. PREPARATIONS FROM DITHIENYL KETONES

A wide range of dithienyl ketones is readily accessible, either from the Friedel-Crafts thenoylation of a thiophene or by oxidation of a secondary alcohol prepared from a thienyl organometallic derivative and a thienyl-aldehyde. The Huang-Minlon/Wolff-Kishner reduction of these ketones is generally very successful, so it is rather surprising that very few dithienylmethanes have been made in this way. The sequence has been used with good results to prepare 5-methyl-<sup>71</sup> and 5,5'-dimethyl-2,2'-dithienylmethane<sup>14</sup> and less successfully, 2,2',5,5'-tetramethyl-3,3'-dithienylmethane.<sup>21</sup> The strongly acidic conditions of the Clemmensen reduction make it of dubious value with thiophene compounds, and in the one reported application to the synthesis of 4,4'-dibromo-3,3'-dithienylmethane the yield was poor.<sup>2</sup>

1,1-Bis(thienyl)alkenes are produced by dehydration of the alcohols that result from the combination of a dithienyl ketone and an organometallic

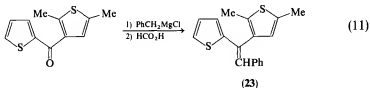
<sup>69</sup> Y. L. Goldfarb and M. S. Kondakova, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, 1235 (1956).

<sup>70</sup> N. M. Löfgren and C. P. Tegner, Swedish Patent 138,064 (1952).

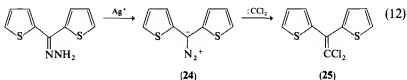
<sup>71</sup> Y. L. Goldfarb and P. A. Konstantinov, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, 1013 (1956).



compound. Buu-Hoi and Hoan<sup>19</sup> obtained 1,1-bis(thienyl)ethenes (e.g., **23**, Eq. 11), and the Reformatsky reaction has been employed by several groups<sup>72-74</sup> in the syntheses of substances of potential pharmacological activity.



An interesting, rather indirect route to a 1,1-bis(2-thienyl)ethene (**25**) from 2,2'-dithienyl ketone involved interaction of the unstable diazo compound **24** and dichlorocarbene (Eq. 12).<sup>75</sup>



### G. REACTION OF A THIENYLMAGNESIUM HALIDE OR THIENYL LITHIUM WITH A THIENYLALDEHYDE OR THIENYL KETONE

Apart from syntheses aimed at producing substances for biological evaluation, which will be discussed later, most work in this area has employed aldehydes rather than ketones. Acidic conditions must be avoided during the isolation of the alcohols, since ethers are readily formed.<sup>47,76</sup> In the great majority of cases the alcohol has been successfully reduced by the lithium aluminum hydride-aluminum chloride method to which we have already referred. Halogen substituents on the thiophene ring (even iodine) survive this procedure. The methods of synthesis discussed in the preceding sections are not suitable for the preparation of unsymmetric dithienylmethanes with free thiophene  $\alpha$ -positions, and it is for these substances that the

<sup>72</sup> N. Shigematsu and G. Hayashi, *Yakugaku Zasshi* **81**, 421 (1961) [*CA* **55**, 7618 (1961)].

<sup>73</sup> R. Kimura, T. Yabuuchi, and Y. Tamura, *Chem. Pharm. Bull.* **8**, 103 (1960).

<sup>74</sup> R. M. Acheson, K. E. MacPhee, P. G. Philpott, and J. A. Barltrop, *J. Chem. Soc.*, 698 (1956).

<sup>75</sup> H. Reimlinger, *Chem. Ber.* **97**, 3503 (1964).

<sup>76</sup> S. Gronowitz and B. Eriksson, *Ark. Kemi* **21**, 335 (1964).

aldehyde-organometallic compound route is particularly valuable. Tables IV (Eq. 13) and V (Eq. 14) present a summary of the results of syntheses of otherwise unobtainable dithienylmethanes.

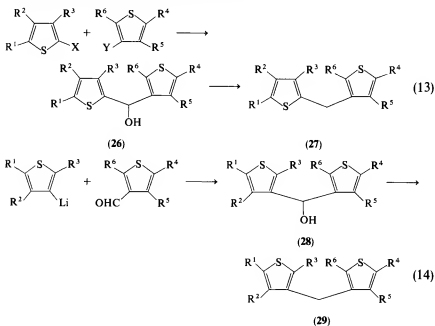


TABLE IV  
PREPARATION OF 2,3'-DITHIENYLMETHANES (26 AND 27)

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	X	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	Y	Yield (%)		Ref.
								26	27	
H	H	Br	Li	H	H	H	CHO	... 47 ...	...	77
H	H	H	CHO	H	H	H	Li	... 44 ...	...	15
H	H	H	CHO	H	H	Me	Li	—	—	78
H	H	Br	Li	H	H	Br	CHO	61	88	2
H	H	Br	CHO	H	Br	H	Li	70	88	2
H	H	H	CHO	H	Br	H	Li	56	86	66
H	H	Br	Li	H	H	H	CHO	63	66	66
Me	Me	I	Li	Me	I	Me	CHO	58	—	79

<sup>77</sup> N. Aggarwal and D. H. W. MacDowell, *Org. Prep. Proced. Int.* **11**, 247 (1979).

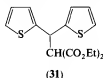
<sup>78</sup> A. G. Giumanini, C. Trombini, G. Lercker, and A. R. Lepley, *J. Org. Chem.* **41**, 2187 (1976).

<sup>79</sup> A. Wiersema and S. Gronowitz, *Acta Chem. Scand.* **24**, 2593 (1970).

TABLE V  
 PREPARATION OF 3,3'-DITHIENYLMETHANES (28 AND 29)

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	Yield (%)		Ref.
						28	29	
H	H	H	H	H	H	68	80	15
H	Br	H	H	Br	H	60	86	2
H	Br	H	H	H	Br	100	75	2
H	Br	H	H	H	H	95	91	66
Me	Me	H	Me	Me	H	91	91	79

Simple thienyl ketones do not appear to have been used in this type of synthesis, but Chirkin and Putokhin<sup>80</sup> reported the formation of 1-aryl-3,3-bis(2-thienyl)propan-1-ones (**30**, Ar = C<sub>6</sub>H<sub>5</sub> or 2-C<sub>4</sub>H<sub>3</sub>S) by conjugate addition of 2-thienylmagnesium bromide to  $\alpha,\beta$ -unsaturated ketones (2-C<sub>4</sub>H<sub>3</sub>S—CH=CH—COAr). In a closely related reaction this Grignard reagent adds to 2-C<sub>4</sub>H<sub>3</sub>S—CH=C(CO<sub>2</sub>Et)<sub>2</sub>, giving rise to an excellent yield (86%) of the substituted malonate **31**.<sup>81</sup> Thenoylformates give dithienylhydroxy



esters on reaction with thienyl Grignard reagents. Methyl 3-thenoylformate, for example, yielded the 2,3'- and 3,3'-dithienylmethane derivatives **32** (46%) and **33** (23%) with 2-thienylmagnesium iodide and 3-thienylmagnesium bromide, respectively.<sup>82</sup> Similarly, ethyl 2-thenoylformate gave a carbinol (55%) which, on reduction with tin(II) chloride–hydrochloric acid, gave an



<sup>80</sup> Y. D. Churkin and N. I. Putokhin, *Zh. Org. Khim.* **1**, 603 (1965) [*CA* **63**, 1762 (1965)].

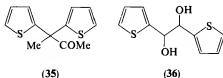
<sup>81</sup> D. Muller, J.-F. Muller, and D. Cagniant, *J. Chem. Res., Synop.*, 328; *J. Chem. Res., Miniprint*, 3673 (1977).

<sup>82</sup> K. Nyberg, B. Östmann, and G. Wallerberg, *Acta Chem. Scand.* **24**, 1590 (1970).

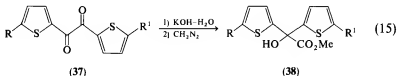
excellent yield of ethyl bis(2-thienyl)acetate (**34a**).<sup>63</sup> The corresponding acid is also satisfactorily reduced by this means, giving **34b** (60%).<sup>83</sup>

## H. MISCELLANEOUS REACTIONS LEADING TO DITHIENYLALKANES

Polarographic reduction of 2-acetylthiophene in tetrahydrofuran–water with sodium perchlorate as electrolyte, followed by distillation, led to a mixture that contained 3,3-bis(2-thienyl)butan-2-one (**35**).<sup>84</sup> In another study<sup>85</sup> it was shown that the pinacol **36** was the sole product if the reduction was carried out in the presence of a weak acid, whereas perchloric acid led to a mixture of **35** and **36**. Reduction of 2-acetylthiophene with aluminum amalgam gave only **35**<sup>86</sup>; finally, it was shown that **36** is very efficiently converted to **35** by mercuric chloride and by sulfuric acid. A pinacol was also obtained from 2-benzoylthiophene, and this, too, rearranged readily to a bis(2-thienyl) derivative,<sup>87</sup> indicating that the 2-thienyl group has a greater migratory aptitude than phenyl.



The base-catalyzed rearrangement of thenils leads to thiophene analogs of benzoic acids. These compounds are rather unstable, but their esters are not, and Schuetz and Nilles<sup>88</sup> obtained good yields of the latter (**38**,  $R = R^1 = H$ ,  $F$ ,  $Cl$ ,  $Me$ ;  $R = H$ ,  $R^1 = Me$ ) from a range of thenils (**37**, Eq. 15).



<sup>83</sup> F. F. Blicke and M. U. Tsao, *J. Am. Chem. Soc.* **66**, 1645 (1944).

<sup>84</sup> C. Caullet, J. M. Bessin, and J. C. Bodard, *C. R. Hebd. Seances Acad. Sci., Ser. C* **261**, 1848 (1965).

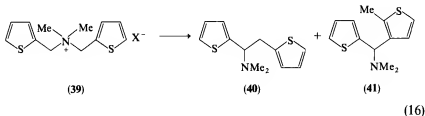
<sup>85</sup> P. Foulatier and C. Caullet, *C. R. Hebd. Seances Acad. Sci., Ser. C* **279**, 25 (1974).

<sup>86</sup> N. D. Heindel, *J. Heterocycl. Chem.* **3**, 379 (1966).

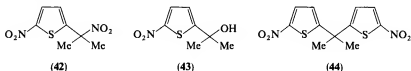
<sup>87</sup> P. Foulatier and J. Salaun, *C. R. Hebd. Seances Acad. Sci., Ser. C* **279**, 779 (1974).

<sup>88</sup> R. D. Schuetz and G. P. Nilles, *J. Org. Chem.* **36**, 2486 (1971).

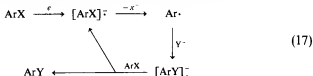
Giumanini *et al.*<sup>78</sup> have studied rearrangements of *N,N*-dimethyl-*N*-bis(2-thienyl)ammonium salts (**39**, X = Cl, I). The two products, **40** and **41** (Eq. 16), arise by the Stevens and Sommelet-Hauser rearrangements, respectively; it was found that the product ratio depended on the nature of the base, the solvent, and the temperature. The highest proportion of the dithienylmethane **41** (75%) in the product was obtained with sodamide in liquid ammonia at  $-45^{\circ}\text{C}$ .



Interaction of 5-nitro-2-iodothiophene with the lithium or tetrabutylammonium salt of 2-nitropropane gives a mixture containing **42** (1–14%), **43** (7–13%), and 2,2-bis(5-nitro-2-thienyl)propane (**44**)<sup>89</sup>; the individual yields depend on the solvent and on the reaction conditions. Probably, **44** arises from **42**, since the latter gives the former when treated with the nitropropane lithium salt.



When aryl halides ( $\text{ArX}$ ) react with nucleophiles ( $\text{Y}^-$ ) in the presence of solvated electrons or under UV irradiation, a radical chain mechanism occurs (Eq. 17). In reactions with an acetone enolate salt, both 2-chloro- and



2-bromothiophene gave a 1:1 product. 3-Bromothiophene, however, gave the 2:1 product, 1,1-bis(3-thienyl)propan-2-one (25%), in addition to the expected 1:1 product, 3-thienylacetone (51%), on reaction with acetone potassium enolate in liquid ammonia under UV irradiation.<sup>90</sup>

<sup>89</sup> P. J. Newcombe and R. K. Norris, *Aust. J. Chem.* **31**, 2463 (1978).

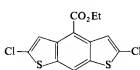
<sup>90</sup> J. F. Bunnett and B. F. Gloor, *Heterocycles* **5**, 377 (1976).

### III. Reactions

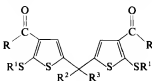
#### A. ELECTROPHILIC SUBSTITUTION

##### 1. Orientation

Most published work on the electrophilic substitution of dithienylalkanes has been concerned with bis(2-thienyl) systems. Substitution invariably takes place at free  $\alpha$ -positions of the thiophene rings to give the 5-substituted and/or 5,5-disubstituted derivative. The little available information about the further substitution of bis(5-substituted-2-thienyl)alkanes suggests that the bridging alkyl group activates the adjacent (3- and 3'-) positions, and only strongly ortho-directing groups at C-5 outweigh this influence. Thus, 5,5'-dichloro-2,2'-dithienylmethane (**4**) gives products (e.g., **45**) via attack at C-3,<sup>15,91</sup> but formylation and acetylation of bis(5-alkylthio-2-thienyl)alkanes takes place at the 4-positions, giving **46** ( $R^1 = \text{Me, Et}$ ;  $R^2 = \text{H, alkyl}$ ;  $R^3 = \text{alkyl}$ ;

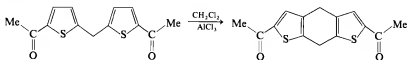


(45)



(46)

$R = \text{H, Me}$ ).<sup>44</sup> When the 5- and 5'-substituents are meta-directing, the preference for further substitution at C-3 is likely to be reinforced. Such substituents are, of course, deactivating, and in the sole reported example of substitution of such a compound the product was formed in very low yield (Eq. 18).<sup>56</sup>



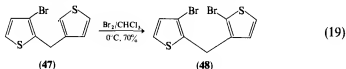
(18)

The most readily substituted positions in 3,3'-dithienylmethane are C-2 and C-2'; for example, mono-<sup>66</sup> and dibromination<sup>2</sup> lead to the 2-bromo (68%) and 2,2'-dibromo compounds (50%).

Information concerning the orientation of electrophilic substitution of 2,3'-dithienylmethanes is sparse. There are no data for the parent substance, but it seems probable that the 2'-position would be the most reactive of the

<sup>91</sup> M. Ahmed, J. Ashby, and O. Meth-Cohn, *Chem. Commun.*, 1094 (1970).

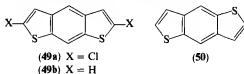
three vacant thiophene  $\alpha$ -positions; this is certainly the case in 3-bromo-2,3'-dithienylmethane (**47**), which gave **48** on bromination (Eq. 19).<sup>2</sup>



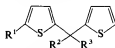
## 2. Vilsmeier and Related Reactions

Application of the Vilsmeier reaction to 2,2'-dithienylmethane gives modest yields of the 5-formyl derivative.<sup>14,41</sup> 2,3'-Dithienylmethane was also formylated, in low yield, but the location of the group was not established.<sup>15</sup> The expected 5'-aldehyde was obtained from 5-methyl-2,2'-dithienylmethane.<sup>71</sup>

The directive influence of substituents in the 5,5'-positions has an interesting outcome in the formylation of 5,5'-dichloro-2,2'-dithienylmethane. Under the conditions employed by Meth-Cohn and co-workers<sup>15</sup> the aldehyde (of uncertain orientation, but probably the 3-isomer) was accompanied by the dithienobenzene **49a** (8%). In similar circumstances 3,3'-dithienylmethane gave **49b** (33%). The intermediacy of the aldehyde in these reactions is supported by the fact that preformed aldehydes give good to excellent yields of dithienobenzenes on treatment with hydrogen bromide or with polyphosphoric acid. For example, 3-formyl-2,2'-dithienylmethane gave **49b** (40%),<sup>67</sup> and 3-formyl-2,3'-dithienylmethane (cyclizing onto an  $\alpha$ -position) afforded **50** in almost quantitative yield.<sup>77</sup>



In general, the yields of aldehydes obtained by Vilsmeier formylation of dithienylmethanes are not good. The same is not true of other bis(2-thienyl)alkanes; for example, the compounds **51a–51c** gave yields of the 5'-aldehyde of 70,<sup>36</sup> 87,<sup>36</sup> and 82%,<sup>39</sup> respectively. The excellent results obtained in these cases suggest that the linking methylene group in dithienyl-

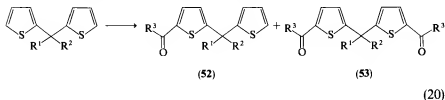


- (51a)  $R^1 = R^2 = R^3 = \text{Me}$   
 (51b)  $R^1 = R^2 = \text{Me}; R^3 = \text{Et}$   
 (51c)  $R^1 = R^2 = \text{Et}; R^3 = n\text{-Pr}$

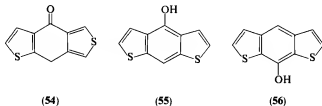
methanes may be entering into reactions with either the reagent or with the product, giving polymeric material. Another difference is that bisformylation does not occur with dithienylmethanes, but is a common feature in other bis(2-thienyl)alkanes with two free thiophene  $\alpha$ -positions. Sy and Maillet,<sup>35</sup> for example, found that dimethylformamide-phosphoryl chloride gave a mixture of the 5-formyl (40%) and 5,5'-diformyl derivatives (25%) from 2,2-bis(2-thienyl)propane. At about the same time it was discovered<sup>92</sup> that very high overall yields of the diformyl compound can be obtained if the formylation is carried out in two distinct stages (isolation of the monoaldehyde is not necessary).

### 3. Acylation

Almost all reports of acylation of dithienylalkanes have involved 2,2'-derivatives with free 5- or 5,5'-positions (Eq. 20); details are compiled in Table VI. The catalysts employed have been those commonly used with thiophenes, i.e., tin(IV) chloride for acid chlorides and anhydrides and polyphosphoric acid for carboxylic acids. Iodine has often been the catalyst for the reaction of dithienylalkanes with acetic anhydride; perchloric acid has also been used.<sup>39</sup> Bisacylation is often observed and can be made the major reaction by use of an excess of reagent.



MacDowell and Wisowaty<sup>66</sup> prepared five dibenzothiophene analogs of anthranol by intramolecular Friedel-Crafts cyclizations of various dithienylmethane acid chlorides. The equilibrium lay in favor of the keto tautomer when any 3,4-fusion of a thiophene ring was involved (e.g., in **54**) and in favor of the enol form in the two cases (**55** and **56**) in which only 2,3-fusion is present.



<sup>92</sup> P. Friedman and P. Allen, *J. Org. Chem.*, **30**, 780 (1965).



TABLE VI  
ACYLATION OF 2,2'-DITHIENYLMETHANE AND  
BIS(2-THIENYL)ALKANES TO GIVE KETONES **52** AND **53**

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Agent <sup>a</sup>	Yield (%)		Ref.
				<b>52</b>	<b>53</b>	
H	H	Me	a	—	46	9, 93
H	H	Me	b	—	—	94
H	H	Et	c	—	56	95
H	H	2-C <sub>4</sub> H <sub>3</sub> S	d <sup>b</sup>	77	—	96
H	H	2-C <sub>4</sub> H <sub>3</sub> S	d <sup>c</sup>	10	—	14
H	H	2-C <sub>4</sub> H <sub>3</sub> S	e	—	98	96
H	H	5-Br-2-C <sub>4</sub> H <sub>2</sub> S	e	—	12	96
H	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	d <sup>d</sup>	72	17	97
H	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	d <sup>e</sup>	17	64	97
H	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	d	—	77	95
H	H	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	d <sup>d</sup>	64	14	97
H	H	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	d <sup>e</sup>	32	46	97
H	H	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> Et	d	—	46	95
H	H	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> H	d <sup>f</sup>	65	—	34
H	Me	Me	a	—	51	9
Me	Me	Me	f	25	64	26, 98
Me	Me	Me	a	—	67	33

<sup>a</sup> Key: a, Ac<sub>2</sub>O/I<sub>2</sub>; b, RCOCl/AlCl<sub>3</sub>; c, (RCO)<sub>2</sub>O/SnCl<sub>4</sub>;

d, RCOCl/SnCl<sub>4</sub>; e, RCO<sub>2</sub>H/PPA; f, Ac<sub>2</sub>O/H<sub>3</sub>PO<sub>4</sub>.

<sup>b</sup> Small quantity of SnCl<sub>4</sub>.

<sup>c</sup> Normal quantity of SnCl<sub>4</sub>.

<sup>d</sup> One equivalent of RCOCl.

<sup>e</sup> Excess of RCOCl.

<sup>f</sup> Initial product saponified.

#### 4. Nitration

The thiophene rings in simple dithienylalkanes possess about the same level of reactivity as those in simple alkylthiophenes. Peter<sup>1</sup> noted a "violent reaction" when 2,2'-dithienylmethane was treated with fuming nitric acid.

<sup>93</sup> B. C. McKusick, U.S. Patent 2,467,439 [CA 43, 6238 (1949)].

<sup>94</sup> N. P. Buu-Hoi, M. Sy, and N. D. Xuong, C. R. Hebd. Seances Acad. Sci., Ser. C 240, 442 (1955).

<sup>95</sup> R. D. Schuetz and R. A. Baldwin, J. Org. Chem. 27, 2841 (1962).

<sup>96</sup> M. Ahmed and O. Meth-Cohn, Chem. Commun., 82 (1968).

<sup>97</sup> Y. L. Goldfarb and M. L. Kirmalova, Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.), 487 (1957).

<sup>98</sup> M. Ahmed and O. Meth-Cohn, Tetrahedron Lett., 1493 (1969).

The nitrating agents of choice for these reactive compounds are copper(II) nitrate-acetic anhydride or fuming nitric acid-acetic anhydride. 5,5'-Dinitration has invariably been observed in the few reported examples [all involving bis(2-thienyl) compounds], i.e., from 2,2'-dithienylmethane<sup>99</sup> (no yield given), 2,2-bis(2-thienyl)propane<sup>89</sup> (76%), and 1,1,1-trichloro-2,2-bis(2-thienyl)ethane<sup>100</sup> (36%); in the last case elimination of hydrogen chloride also occurred if the nitration was carried out at higher temperatures (20°–30°C), giving 1,1-dichloro-2,2-bis(5-nitro-2-thienyl)ethene (37%).

### 5. Bromination

No chloro- or iododithienylalkanes have been prepared by direct halogenation. The brominations reported have generally been effected by mild reagents, under mild conditions, although Peter<sup>1</sup> obtained a crystalline hexabromo derivative from 1,1,1-trichloro-2,2-bis(2-thienyl)ethane by refluxing it with bromine. In a study of the bromination of 2,2'-dithienylmethane Goldfarb and Kirmalova<sup>16</sup> found that acidified potassium bromide-potassium bromate gave mainly the 5-bromo (64%) or 5,5'-dibromo derivative (68%) with 1 and 2 equivalents of reagent, respectively. *N*-Bromosuccinimide, expected to bring about some halogenation at the methylene bridge, instead gave as the major product 5-bromo-2,2'-dithienylmethane. The bromination<sup>2,66</sup> of 3,3'-dithienylmethane has already been referred to (Section III.A,1).

### 6. Other Electrophilic Substitution Reactions

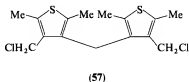
Apart from the reactions discussed above, only chloromethylation has received more than a single mention. 2,2'-Dithienylmethane itself can be chloromethylated (at C-5); the product was converted directly to the diethylamine.<sup>101</sup> A linear tetrathiophene (9,  $n = 2$ ) was a by-product. Bischloromethylation took place in both 1,1-bis(2-thienyl)ethane<sup>101</sup> and 2,2',5,5'-tetramethyl-3,3'-dithienylmethane<sup>21</sup> with chloromethyl ether; in the latter case the yield of bischloromethyl derivative **57** was very high (94%). Treatment of the arylidithienylmethanes **58** (Ar = phenyl, and 2-, 3-, and 4-nitrophenyl) with fuming sulfuric acid yielded tris(sulfonic acids) (isolated

<sup>99</sup> Y. Inaba, G. Kimura, and S. Umicke, Japanese Patent 9586 (1962). [*CA* **59**, 9988 (1963)].

<sup>100</sup> P. Truitt, *J. Org. Chem.* **26**, 5250 (1961).

<sup>101</sup> P. A. Konstantinov, L. V. Semerenko, K. M. Suvorova, E. N. Bondar, and Y. L. Goldfarb, *Khim. Geterotsikl. Soedin.*, 230 (1968) [*CA* **70**, 57554 (1969)].

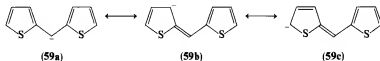
as their barium salts).<sup>29</sup> Probably, two of the sulfonic acid groups are at the thiophene 5-positions.



## B. LITHIATION

In dithienylalkanes, as in simple thiophenes, the ease of replacement of atoms by lithium is  $\alpha$ -halogen  $>$   $\beta$ -halogen  $>$   $\alpha$ -hydrogen  $>$   $\beta$ -hydrogen. By suitable selection of starting material and reaction conditions it is therefore possible to obtain a dithienylalkane lithiated at any desired position. For example, 2,2'-dithienylmethane is lithiated at C-5, whereas 3-bromo-2,2'-dithienylmethane gives the 3-lithio derivative; these intermediates lead to good yields of 5,5'-diformyl-<sup>26</sup> and 3-formyl-2,2'-dithienylmethane,<sup>67</sup> respectively. In all cases an alkyl lithium (usually butyllithium) has been employed as lithiating agent.

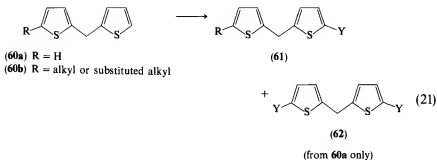
An interesting possibility with dithienylalkanes carrying a proton on the linking carbon atom is the formation of an anion at that site; it might be expected that such an ion would be extensively stabilized by delocalization of the charge (e.g., **59a**–**59c**). In fact, no product arising by attack of a dithienylalkyl ion, such as **59a**, has been observed in lithiation reactions. Goldfarb and Kirmalova<sup>41</sup> reasoned that central anion formation might be more favored if all the thiophene  $\alpha$ -positions were blocked, as in 5,5'-dimethyl-2,2'-dithienylmethane. However, in this case lithiation proceeded very inefficiently (judging from the very low yield of carbonated product) and took place at one of the thiophene  $\beta$ -positions (exact location unknown).



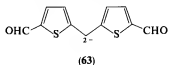
Ahmed and Meth-Cohn<sup>26,96</sup> found the lithiation of 2,2'-dithienylmethane to be temperature dependent. Below  $-10^{\circ}\text{C}$  monolithiation and above  $+5^{\circ}\text{C}$  dilithiation were observed; at intermediate temperatures mixtures were obtained. Once formed, the lithio derivatives of dithienylalkanes behave unexceptionally. A summary of results from 2,2'-dithienylmethanes is presented in Table VII (Eq. 21).

TABLE VII  
 SUBSTITUTION PRODUCTS (**61** and **62**) FROM LITHIATED 2,2'-DITHIENYLALKANE INTERMEDIATES

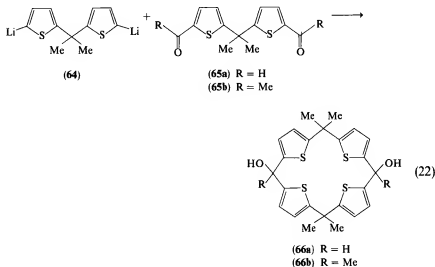
R	Moles BuLi	Reagent <sup>a</sup>	Y	Yield (%)		Ref.
				<b>61</b>	<b>62</b>	
H	2	a	CHO	—	75	26
H	1	b	CO <sub>2</sub> H	70	—	43
H	2	b	CO <sub>2</sub> H	—	"low"	43
H	2	b	CO <sub>2</sub> H	—	70	26
H	1	c	CH <sub>2</sub> CH <sub>2</sub> OH	74	13	43
H	2	c	CH <sub>2</sub> CH <sub>2</sub> OH	12	77	43
H	1	d	C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>	47	—	14
CH <sub>3</sub>	1	a	CHO	39	—	41
CH <sub>3</sub>	1	b	CO <sub>2</sub> H	31	—	41
CH <sub>3</sub>	1	c	CH <sub>2</sub> CH <sub>2</sub> OH	59	—	41
(CH <sub>2</sub> ) <sub>2</sub> OH	2	b	CO <sub>2</sub> H	32	—	102

<sup>a</sup> Key: a, DMF; b, CO<sub>2</sub>; c,  $\text{CH}_2=\text{O}-\text{CH}_2$ ; d, C<sub>4</sub>H<sub>9</sub>SCH<sub>2</sub>Cl.


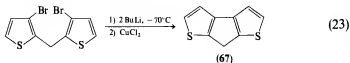
In approaches to thiophene analogs of porphyrins Ahmed and Meth-Cohn<sup>26</sup> attempted to react the dilithio derivative of 2,2'-dithienylmethane (i.e., **62**, Y = Li) with the dialdehyde (**62**, Y = CHO) under high-dilution conditions. No reaction took place, however, and the failure was ascribed to an exchange reaction giving the dianion **63** from the aldehyde; this would


<sup>102</sup> Y. L. Goldfarb and M. L. Kirmalova, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, 509 (1955).

revert to the starting material on work-up. The problem was overcome by use of the analogous bis(2-thienyl)propanes **64** and **65a,b**, from which low yields of the required cyclic substances **66a** (4.2%) and **66b** (2.5%) were obtained (Eq. 22).



The halogen-metal exchange reaction has been used almost exclusively for the formation of dithienylmethanes lithiated at thiophene  $\beta$ -positions; these derivatives give acceptable yields of aldehydes<sup>77</sup> on reaction with dimethylformamide and of acids on carbonation.<sup>66</sup> Particular use has been made of bis- $\beta$ -lithiated compounds for the preparation (via oxidative coupling) of thiophene analogs of fluorenes.<sup>3,67</sup> The synthesis of cyclopenta-[1,2-*b*:4,3-*b'*]dithiophene (**67**) is typical (Eq. 23).

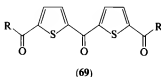
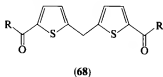


### C. CENTRAL METHYLENE OR METHINE ACTIVITY

The possibility of forming stabilized anions (e.g., **59a–59c**) on treatment with strong bases has already been referred to, and it was noted that the various reported reactions with butyllithium had given no indication of

central methylene group reactivity. In contrast, the potassium derivative of 2,2'-dithienylmethane, prepared by treatment of the substance with potassium amide in liquid ammonia, gave only ethyl bis(2-thienyl)acetate (the product of reaction at the methylene group) when treated with diethyl carbonate.<sup>103</sup> Generally, however, suitably located electron-withdrawing substituents are necessary before anion formation is observed at the linking carbon atom.

One reaction of unsubstituted dithienylmethanes that must involve anionic intermediates is base-catalyzed oxidation by oxygen, which takes place in the presence of potassium *tert*-butoxide in a mixture of dimethyl sulfoxide (DMSO) and *tert*-butyl alcohol. 2,2'-Dithienylmethane gave di-2-thienyl ketone (81%),<sup>104</sup> and 2,3'-dithienylmethane yielded 2-(3-thienyl)thiophene (88%).<sup>105</sup> Although 3,3'-dithienylmethane failed to react under the same conditions, an increase in the proportion of DMSO in the solvent led to a high yield of ketone.<sup>105</sup> The higher reactivities of the compounds containing a 2-substituted thiophene ring were ascribed to the greater possibility of charge delocalization. Certainly oxidation proceeds with great ease when electron-withdrawing substituents are present in positions where they can act on the methylene group; substances of general form **68** give intense blue colors with alkali metal hydroxides in alcohol solution and are oxidized to **69** in very high yields by the passage of air.



Oxidation with air is generally much more efficient than with other oxidants, e.g., from **68** ( $R = 2$ -thienyl, 96%; 65% with  $MnO_2$ <sup>26,96</sup>) and from **68** ( $R = Me$ , 88%; 68% with  $CrO_3-HOAc$ <sup>9,93</sup>). As expected, hypochlorite oxidation of the acetyl groups of **68** ( $R = Me$ ) was accompanied by further oxidation, giving **69** ( $R = OH$ ).<sup>9,93</sup>

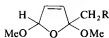
The electrochemical oxidation of 2-furyl-2-thienylmethane in methanol resulted in loss of aromaticity of the furan ring and gave **70** ( $R = 2$ -thienyl). The reaction took a different course with 2,2'-dithienylmethane, which oxidized at the methylene group to give methoxybis(2-thienyl)methane (**71**) and di-2-thienyl ketone.<sup>106</sup>

<sup>103</sup> N. Löfgren and C. P. Tegner, *Acta Chem. Scand.* **6**, 1020 (1952).

<sup>104</sup> E. T. Strom, G. A. Russell, and J. H. Schoeb, *J. Am. Chem. Soc.* **88**, 2004 (1966).

<sup>105</sup> G. Rawson and H. Wynberg, *Recl. Trav. Chim. Pays-Bas* **90**, 39 (1971).

<sup>106</sup> J. Srogl, M. Janda, I. Stibor, and Z. Salajka, *Collect. Czech. Chem. Commun.* **42**, 1361 (1977).

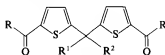


(70)



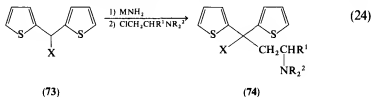
(71)

The use of anions from compounds **68** as nucleophiles in typical carbanion reactions has received almost no attention, although it has been shown<sup>26,96</sup> that such reactions are possible. The compounds **72c–72e** were obtained by reaction of the mono-**72a** or disodio derivative **72b** of **68** ( $R = 2\text{-thienyl}$ ) with the appropriate alkyl halide.

(72)  $R = 2\text{-thienyl}$ 

- a:  $R^1 = H$ ;  $R^2 = Na$   
 b:  $R^1 = R^2 = Na$   
 c:  $R^1 = H$ ;  $R^2 = Me$  (77%)  
 d:  $R^1 = R^2 = Me$  (68%)  
 e:  $R^1 R^2 = -(CH_2)_4-$  (76%)

When the linking carbon itself bears an electron-withdrawing substituent, dithienylalkane derivatives behave normally in respect to anion generation; the bases have been alkali metal amides, and yields have been reasonable in spite of the bulky carbanion substituents. The sodium salt of ethyl bis(2-thienyl)acetate (**73**,  $X = CO_2Et$ ) gave the expected products (**74**) with 1-chloro-2-*N*-morpholinoethane<sup>103</sup> and with a variety of other 1-chloro-2-*N,N*-dialkylaminoethanes and -propanes<sup>63</sup> (Eq. 24). Reaction of 2-chloro-

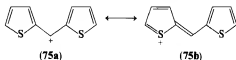


propylamine with the lithium derivative of **73** ( $X = CN$ ) was accompanied by some rearrangement of the alkyl chain.<sup>107</sup>

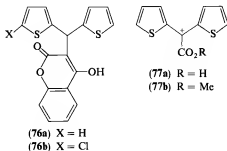
The same considerations concerning delocalization of charge in dithienylalkane anions can be applied to the comparable cationic derivatives; in

<sup>107</sup> E. A. Schildknecht and E. V. Brown, *J. Am. Chem. Soc.* **77**, 954 (1955).

these cases the sulfur atom should also participate (canonical form **75b**).



The very stable nature of such cations when amino groups are suitably placed on the thiophene rings, as in **18** and **19**, has already been mentioned. Ion **75** and the related 5-chloro species [both generated from the appropriate bis(2-thienyl)methanol] behaved as electrophiles toward 4-hydroxycoumarin, giving **76a** (74%) and **76b** (66%), respectively.<sup>108</sup>



Nilles and Schuetz<sup>109</sup> obtained ions **77a** and **77b** by treatment of bis(2-thienyl)glycolic acid (or its methyl ester) with chlorosulfonic acid. The authors conclude that the NMR spectra of the ions are consistent with participation of the thiophene rings in stabilizing the positive charge.

#### D. REACTIONS OF SUBSTITUENTS

Substituents on dithienylalkanes behave normally. Certain reactions of readily accessible derivatives have been well studied; others have received scarcely any attention.

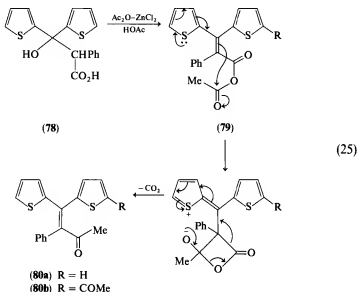
The halogenated dithienylalkanes arising from condensation of thiophenes with halogenated aldehydes (see Tables I and II) have been used to prepare a variety of derivatives. Hydrolysis of the trichloromethyl group leads to carboxylic acids,<sup>41,107</sup> and bis(2-acetyl-4-thienyl)dichloromethane gives the ketone.<sup>56</sup> On treatment with potassium hydroxide in ethanol, the halogenoalkanes eliminate hydrogen halide<sup>1,24,27,42,55</sup> to give bis(thienyl)alkenes.

<sup>108</sup> T. Kralt, J. P. L. Bots, H. D. Moed, and E. J. Ariens, *Recl. Trav. Chim. Pays-Bas* **86**, 961 (1967).

<sup>109</sup> G. P. Nilles and R. D. Schuetz, *Tetrahedron Lett.*, 4313 (1969).



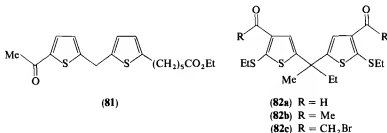
Alkenes are also readily formed by dehydration of hydroxybis(thienyl)alkanes (see Section IV). One reaction of particular interest is the formation of the acetylated alkenes **80a** and **80b** on treatment of the carbinol **78** with acetic anhydride–zinc chloride<sup>110</sup>; a possible mechanism involves the mixed anhydride **79** (Eq. 25).



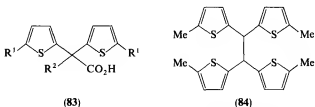
The Wolff–Kishner reduction of aldehydes,<sup>35,36,41</sup> of acetyl groups on a thiophene ring<sup>23,39</sup> and in a side chain,<sup>111</sup> of a thenoyl group,<sup>14</sup> and of  $\text{CO}(\text{CH}_2)_n\text{CO}_2\text{R}$ <sup>34,95,97,102</sup> proceeded in generally good yields. Silver oxide oxidation of aldehydes<sup>39,44,92</sup> takes place normally. Hypohalite oxidation of methyl ketones leads, as usual, to carboxylic acids. When the methylene group linking the two thiophene rings is substituted, there are no complications,<sup>33,44</sup> but in dithienylmethanes the possibility of simultaneous oxidation of the methylene group also exists. Such oxidation was reported to occur with **68** (R = Me)<sup>9,93</sup> using hypochlorite, but others made no mention of such oxidation of **68** (R = Me)<sup>94</sup> or of **81**<sup>34</sup> with hypobromite, although no yield of acid was given in either case. A low yield (5%) of 2,2-bis(2-thienyl)propionic acid was obtained by hypochlorite action on 3,3-bis(2-thienyl)butan-2-one (**35**).<sup>40</sup> The formation of Schiff bases and of acetals from **82a** and the bromination of **82b**, giving **82c**, have been reported by Goldfarb *et al.*<sup>44</sup>

<sup>110</sup> T. Ivanov and D. Mondeshka, *J. Prakt. Chem.* [2] **315**, 993 (1973).

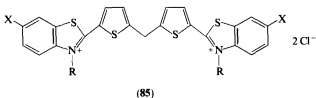
<sup>111</sup> M. Sy and M. Maillet, *C. R. Hebd. Seances Acad. Sci., Ser. C* **262**, 151 (1966).



Grignard reagents were formed with difficulty from both 5-bromo- and 5,5'-dibromo-2,2'-dithienylmethane; they gave acids (71 and 81%, respectively) on carbonation.<sup>16</sup> A carboxyl group attached to a thiophene ring has been decarboxylated with copper-quinoline (80%)<sup>39</sup>; bis(2-thienyl)alkanoic acids of general formula **83** decarboxylate quite readily on heating.<sup>40,107</sup> In one case (**83**, R<sup>1</sup> = Me; R<sup>2</sup> = H) the expected decarboxylation product was accompanied by a little of the dimer **84**.



The bis(acid chloride) of 2,2'-dithienylmethane-5,5'-dicarboxylic acid condenses with 5-substituted 2-alkylaminothiophenols to give cyanine dyes of general structure **85**.<sup>112</sup>



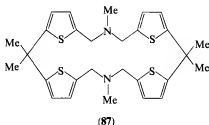
Bromination of **86a** by *N*-bromosuccinimide took place at the allylic position rather than on the thiophene rings; the resulting bromomethyl compound (**86b**), on reaction with a variety of secondary amines, gives products (**86c**) with analgesic and antitussive properties.<sup>113</sup> Nucleophilic substitution of chlorine from chloromethyl derivatives has been effected by

<sup>112</sup> A. A. Shulezhko, I. T. Rozhdstvenskaya, and A. I. Kiprianov, *Zh. Org. Khim.* **6**, 2118 (1970) [*CA* **74**, 43509 (1971)].

<sup>113</sup> N. Shigematsu and G. Hayashi, *Yakugaku Zasshi* **81**, 421 (1961) [*CA* **55**, 7618 (1961)].

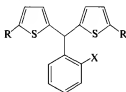


- (86a) X = H  
 (86b) X = Br  
 (86c) X = NR<sup>1</sup>R<sup>2</sup>

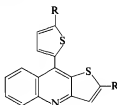


(87)

cyanide,<sup>49</sup> malonate,<sup>49</sup> phthalimide,<sup>50</sup> and ethoxide<sup>50</sup> ions and by a variety of secondary amines.<sup>101</sup> An example of special interest involved the interaction of a bischloromethyl and a bismethylamino compound under high-dilution conditions to give the macrocycle **87**. Lithium aluminum hydride reduction of **31** gave an excellent yield (87%) of the bis primary alcohol; this was converted, via the dibromide and dinitrile, to the related substituted glutaric acid.<sup>81</sup> Reduction of 2-, 3-, and 4-nitrophenylbis(2-thienyl)methanes to the amines has been achieved by the use of zinc-hydrochloric acid,<sup>29</sup> and 2-nitro- (**88a**) and 2-azidophenylbis(5-alkyl-2-thienyl)methanes (**88b**, R = H, Me, Et, *t*-Bu) have been subjected to nitrene-producing processes.<sup>31,114</sup> Nitrene insertion via an aziridine took place, giving, among other products, the benzothienopyridines **89**.



- (88a) X = NO<sub>2</sub>  
 (88b) X = N<sub>3</sub>



(89)

### E. DESULFURIZATION

The reductive desulfurization of bis(2-thienyl)alkane derivatives with Raney nickel has been used for the synthesis of a variety of compounds; some results are collected in Table VIII (Eq. 26). Acids are best desulfurized in aqueous base, and for neutral substances ethanol is the solvent of choice. As usual, a large excess of nickel is required; in one case<sup>111</sup> a small amount of product resulting from the desulfurization of only one thiophene ring

<sup>114</sup> G. Jones, C. Keates, I. Kladko, and P. Radley, *Tetrahedron Lett.*, 1445 (1979).

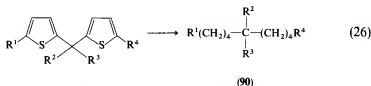
TABLE VIII  
 PRODUCTS (90) FROM THE DESULFURIZATION OF BIS(2-THIENYL)ALKANE DERIVATIVES

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Yield (%)	Ref.
H	H	H	H	59	14
H	CH <sub>3</sub>	CH <sub>3</sub>	H	60	37, 111
H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	H	58	37
H	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H	55	37, 111
H	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	H	55	37, 111
H	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	55	37, 111
H	CH <sub>3</sub>	CH <sub>2</sub> Cl <sup>a</sup>	H	50	40
H	H	H	CHO <sup>b</sup>	35	14
H	CH <sub>3</sub>	COCH <sub>3</sub>	H	—	40
H	H	H	(CH <sub>2</sub> ) <sub>2</sub> OH	76	43
H	H	H	CO <sub>2</sub> H	63	43
H	H	H	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H	66	97
H	H	H	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> H	73	97
H	CH <sub>3</sub>	CO <sub>2</sub> H	H	—	40
CH <sub>3</sub>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	CH <sub>3</sub>	—	111
CH <sub>3</sub>	H	H	CHO <sup>b</sup>	64	71
CH <sub>3</sub>	H	H	(CH <sub>2</sub> ) <sub>2</sub> OH	—	41
CH <sub>3</sub>	H	H	CO <sub>2</sub> H	69	41
C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	H	50	39
(CH <sub>2</sub> ) <sub>2</sub> OH	H	H	(CH <sub>2</sub> ) <sub>2</sub> OH	80	43
(CH <sub>2</sub> ) <sub>2</sub> OH	H	H	CO <sub>2</sub> H	94	102
(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H	H	H	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H	—	97
(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H	H	H	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H	"low"	102
(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> H	H	H	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> H	69	97
CO <sub>2</sub> H	H	H	CO <sub>2</sub> H	—	94
CO <sub>2</sub> H	H	H	(CH <sub>2</sub> ) <sub>5</sub> CO <sub>2</sub> H	65	34
CO <sub>2</sub> H	CH <sub>3</sub>	CH <sub>3</sub>	CO <sub>2</sub> H	93	33
CH <sub>3</sub> CO	H	H	CH <sub>3</sub> CO	90	115
CH <sub>2</sub> N(CH <sub>3</sub> )COCH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>2</sub> N(CH <sub>3</sub> )COCH <sub>3</sub>	37	101

<sup>a</sup> Reduced to CH<sub>3</sub>.

<sup>b</sup> Reduced to CH<sub>2</sub>OH.

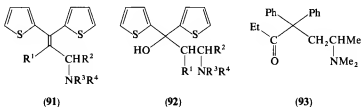
was isolated when insufficient nickel was used. One desulfurization that does not lend itself to tabular presentation is that of the macrocycle **11**, which gave an almost quantitative yield of 1,2,4,5,7,8-hexaethylcyclononane.<sup>22</sup>



<sup>115</sup> G. Kimura, S. Kaichi, M. Koshi, and Y. Inaba, *J. Synth. Org. Chem., Jpn.* **22**, 461 (1964).

#### IV. Substances of Biological Interest

Interest in dithienylalkanes of potential pharmacological importance was aroused by the discovery that some 3-dialkylamino-1,1-bis(2-thienyl)but-1-enes possess analgesic activity.<sup>116</sup> Compounds **91**, termed thiambutenes, are prepared by dehydration of carbinols of general formula **92**. Considerable variations in the substituents have been made in the search for greater activity and for a reduction in undesirable side effects; often, these variants have both analgesic and antitussive properties. Substances with obvious structural similarities to **91** and **92**, namely, the thiophene analog of methadone (**93**) and of isomethadone, have also been prepared.<sup>63,107</sup>



The earlier work in this area has been admirably covered by Martin-Smith and Reid<sup>117</sup> in their review of biological activity in compounds possessing thiophene rings. The following is a survey of the literature from 1959 to the present, although a few earlier references are included.

The usual synthesis of the carbinols **92** is carried out by reaction of an ester with a thienyllithium or Grignard reagent; an alternative approach<sup>118</sup> (from a dithienyl ketone and organometallic compound) has been used recently, however. Dehydration to the thiambutene is most often achieved by treatment with hydrogen chloride in a solvent (normally ethanol or acetic acid), but it has been found that trifluoroacetic acid gives the same result under very mild conditions.<sup>119</sup>

Table IX contains the structures of some of the carbinols (**94**) that have been prepared by reaction of 2-thienylorganometallic compounds with esters; in almost every case dehydration of the carbinol was also reported. Many of the compounds listed here and the alkenes derived from them are anti-histaminic, anticholinergic, or spasmolytic. However, not all the papers and patents referred to give details of biological evaluation, so no survey of biological activity is attempted.

<sup>116</sup> D. W. Adamson and A. F. Green, *Nature (London)* **165**, 122 (1950).

<sup>117</sup> M. Martin-Smith and S. T. Reid, *J. Med. Pharm. Chem.* **1**, 311–315, 537–542 (1959).

<sup>118</sup> J. Engel, A. Kleeman, and K. Thieme, *Ger. Offen.* 3,000,915 [*CA* **93**, 220602 (1980)].

<sup>119</sup> R. B. Moffett and G. N. Evenson, *Org. Prep. Proced. Int.* **11**, 53 (1979).

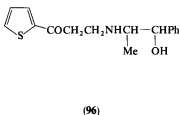
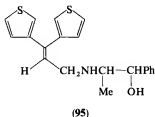
TABLE IX  
CARBINOLS (C<sub>4</sub>H<sub>8</sub>S)<sub>2</sub>CR(OH) (94) PREPARED FROM  
2-THIENYL NUCLEOPHILES AND ESTERS

R	Ref.
CH <sub>2</sub> CHMeNMe <sub>2</sub>	120
CH <sub>2</sub> CHMe- <i>N</i> -piperidyl	121-123
CH <sub>2</sub> CH <sub>2</sub> - <i>N</i> -piperidyl	124
CH <sub>2</sub> CH <sub>2</sub> - <i>N,N'</i> -1- <i>R</i> -piperazyl (R = Me, Et)	124
CH <sub>2</sub> CH <sub>2</sub> - <i>N</i> -(2-Me-pyrrolidyl)	125
CH <sub>2</sub> -2-( <i>N</i> -Me-piperidyl)	126
CHMeCH <sub>2</sub> - <i>N</i> -pyrrolidyl	119, 127
3-( <i>N</i> -Me-piperidyl)	128
4-(NR-piperidyl) (R = alkyl- <i>O</i> -alkyl, alkenyl- <i>O</i> -alkyl)	129
4-(N <sup>+</sup> [Me]R-piperidyl) (R = Me, Et)	130
3-(5-OH-NR-piperidyl) (R = alkyl)	131
3-(5-OR <sup>1</sup> -NR <sup>2</sup> -piperidyl) (R <sup>1</sup> , R <sup>2</sup> = alkyl)	132, 133
3-(2-Me-NR-pyrrolidyl) (R = Me, Et)	125
3-Quinuclidyl	134, 135
1-, 2-, and 3-quinolizidyl	136-139
1-, 2-, and 3-(NMe-quinolizidyl)	140
3-(5-OMe-NMe <sub>2</sub> -piperidyl) <sup>a</sup>	141, 142
1-, 2-, and 3-(NR-quinolizidyl) <sup>a</sup> (R = Me, Et)	139, 143

<sup>a</sup> Derivative of the dehydration product of 94.

- <sup>120</sup> T. Kametani and Y. Akazawa, *J. Pharm. Soc. Jpn.* **73**, 649 (1953) [*CA* **48**, 5175 (1954)].  
<sup>121</sup> R. Kimura and T. Yabuuchi, *Chem. Pharm. Bull.* **7**, 171 (1959).  
<sup>122</sup> R. Kimura, M. Ogawa, and T. Yabuuchi, *Chem. Pharm. Bull.* **7**, 175 (1959).  
<sup>123</sup> Y. Kase, T. Yuizono, T. Yamasaki, T. Yamada, S. I. M. Tamiya, and I. Kondo, *Chem. Pharm. Bull.* **7**, 372 (1959).  
<sup>124</sup> R. Kimura, Y. Tamura, and T. Yabuuchi, Japanese Patent 4085 (1964) [*CA* **61**, 5668 (1964)].  
<sup>125</sup> S. Ohki, T. Azuma, and Y. Nagase, *Yakugaku Zasshi* **89**, 633 (1969) [*CA* **71**, 61110 (1969)].  
<sup>126</sup> N. Sugimoto and S. Saito, *J. Pharm. Soc. Jpn.* **73**, 757 (1953) [*CA* **48**, 9367 (1954)].  
<sup>127</sup> R. B. Moffett, R. E. Strube, and L. Skaletzky, *J. Med. Chem.* **14**, 1088 (1971).  
<sup>128</sup> A. A. Ponomarev and N. I. Martemyanova, *Khim. Geterotsikl. Soedin.*, 174 (1967) [*CA* **67**, 73501 (1967)].  
<sup>129</sup> J. Engel, A. Kleeman, U. Achterrath-Tuckermann, and K. Thieme, Ger. Offen. 3,000,923 [*CA* **93**, 220601 (1980)].  
<sup>130</sup> E. Koshinaka, S. Kurata, N. Ogawa, T. Yamagishi, and H. Kato, Japanese Patent 145,673 (1979) [*CA* **92**, 198261 (1980)].  
<sup>131</sup> M. Kazawa, T. Kanno, H. Tamaki, and T. Ikeo, Japanese Patent 31675 (1974) [*CA* **81**, 37483 (1974)].  
<sup>132</sup> M. Kawazu, T. Kanno, S. Saito, and H. Tamaki, Ger. Offen. 2,128,808 [*CA* **76**, 59458 (1972)].

Alkenes and carbinols of the form **91** and **92**, but with 3- rather than 2-thienyl substitution, are rare; however, one substance in this class (Tinofedrine, **95**)<sup>144</sup> has received attention in the last few years. This and related compounds have been reviewed recently;<sup>145</sup> Tinofedrine labeled with tritium at the allyl methylene and its neighboring vinyl carbon atom has been synthesized.<sup>146</sup> The 2,2'-<sup>147,148</sup> and 2,3'-thiophene-substituted counterparts<sup>148</sup> of Tinofedrine have been prepared from 2-thienylmagnesium



bromide and **96** and its 3-thienyl isomer, respectively. Esters (**97**) of bis-(thienyl)glycolic acids with a variety of amino alcohols have been prepared,

<sup>133</sup> M. Kawazu, T. Kanno, H. Tamaki, T. Ikeo, and S. Harigaya, Japanese Patent 31676 (1974) [CA 81, 49581 (1974)].

<sup>134</sup> E. E. Mikhlin, A. D. Yanina, V. Y. Vorobeva, N. A. Komarova, and L. N. Yakhontov, *Khim. Geterotsikl. Soedin.*, 935 (1976) [CA 85, 159850 (1976)].

<sup>135</sup> E. E. Mikhlin, V. A. Vorobeva, N. A. Komarova, I. M. Sharapov, A. I. Polezhaeva, M. D. Mashkovski, and L. N. Yakhontov, *Khim.-Farm. Zh.* 10, 56 (1976) [CA 86, 155489 (1977)].

<sup>136</sup> E. Koshinaka, S. Kurata, O. Nobuo, T. Yamagishi, and H. Kato, Japanese Patent 115,395 (1979) [CA 92, 110875 (1980)].

<sup>137</sup> E. Koshinaka, S. Kurata, N. Ogawa, and H. Kato, Japanese Patent 88,292 (1979) [CA 92, 76317 (1980)].

<sup>138</sup> E. Koshinaka, S. Kurata, N. Ogawa, T. Yamagishi, and H. Kato, Japanese Patent 103,894 (1979) [CA 92, 128759 (1980)].

<sup>139</sup> E. Koshinaka, N. Ogawa, S. Kurata, K. Yamagishi, S. Kubo, I. Mitsubara, and H. Kato, *Chem. Pharm. Bull.* 27, 1454 (1979).

<sup>140</sup> E. Koshinaka, N. Ogawa, K. Yamagishi, H. Kato, and M. Hanoaka, *J. Pharm. Soc. Jpn.* 100, 100 (1980).

<sup>141</sup> French Patent 2,100,750 [CA 77, 164489 (1972)].

<sup>142</sup> T. Meshi, S. Nakamura, and T. Kanno, *Chem. Pharm. Bull.* 21, 1709 (1973).

<sup>143</sup> E. Koshinaka, S. Kurata, N. Ogawa, T. Yamagishi, and H. Kato, Japanese Patent 103,895 (1979) [CA 92, 128758 (1980)].

<sup>144</sup> K. Thiele, K. Posselt, and H. Offermanns, *Arzneim.-Forsch.* 28, 2047 (1978).

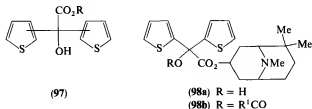
<sup>145</sup> K. Thiele, K. Posselt, H. Offermanns, and K. Thieme, *Arzneim.-Forsch.* 30, 747 (1980).

<sup>146</sup> A. Saus and K. Posselt, *Arzneim.-Forsch.* 30, 917 (1980).

<sup>147</sup> K. Thiele, K. Posselt, A. Gross, and A. W. Schuler, *Chim. Ther.* 4, 228 (1969).

<sup>148</sup> K. Thiele and K. Posselt, Ger. Offen. 1,921,453 [CA 74, 76320 (1971)].

generally by transesterification of the methyl ester. Compounds of this type include the esters of borneol and of tropine with both bis(2-thienyl)- and bis(3-thienyl)glycolic acids,<sup>82</sup> of quinuclidinol with the bis(2-thienyl),<sup>82,149</sup> 2-thienyl-3-thienyl,<sup>82</sup> and bis(3-thienyl)glycolic<sup>82</sup> acids, and of 3-<sup>149,150</sup> and 4-piperidinol<sup>167</sup> with both the symmetric glycolic acids. Attempts have been made to correlate the anticholinergic activity of the quinuclidyl esters with the hydrogen bonding in them,<sup>151</sup> and rate constants for the hydrolysis of these and of the piperidyl esters have been determined in an effort to



establish structure-activity relationships.<sup>149</sup> Compound **98a** shows anti-Parkinson activity,<sup>152</sup> and its acylated derivatives **98b** ( $R^1 = \text{Me, Et, } n\text{-Pr}$ ) are anticholinergic<sup>153</sup>; the metabolic fate of **98a** in the rat has been studied.<sup>154</sup>

The amide of bis(2-thienyl)glycolic acid with 2-(*N*-pyrrolidyl)ethylmethylamine and its methyl quaternary ammonium hydroxide showed spasmolytic activity in mice.<sup>155</sup> Esters of 3,3-bis(2-thienyl)propenoic acid and 2-*tert*-aminoethanols **99** ( $X = \text{OCH}_2\text{CH}_2\text{NR}^2$ ) were obtained both by dehydration of the hydroxy ester **100** ( $X = \text{OCH}_2\text{CH}_2\text{NR}^2$ )<sup>156</sup> and by esterification of unsaturated acid **99** ( $X = \text{OH}$ ).<sup>157</sup> These amino esters showed analgesic, antispasmodic, and antitussive activity. Amides **99** ( $X = \text{NHAr}$ ) were synthesized by reaction of the appropriate primary aromatic

<sup>149</sup> G. Wallerberg and B. Östman, *Acta Chem. Scand.* **30**, 900 (1976).

<sup>150</sup> R. D. Schuetz and G. P. Nilles, *J. Med. Chem.* **13**, 1249 (1970).

<sup>151</sup> L. Larsson, M. Wallensteen, G. Wallerberg, and B. Östman, *Acta Pharm. Suec.* **11**, 304 (1974) [*CA* **81**, 104467 (1974)].

<sup>152</sup> M. Otsuka, S. Nakamura, and Y. Sato, *J. Pharm. Soc. Jpn.* **92**, 986 (1972) [*CA* **77**, 147420 (1972)].

<sup>153</sup> M. Yoneda, T. Ishiwara, T. Kobayashi, K. Omura, Y. Kojima, and N. Nose, Japanese Patent 8,635 (1973) [*CA* **79**, 31904 (1973)].

<sup>154</sup> T. Meshi, S. Nakamura, and Y. Sato, *Chem. Pharm. Bull.* **20**, 1687 (1972).

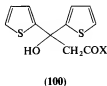
<sup>155</sup> F. Clemence, O. LeMartret, R. Fournex, G. Plassard, and M. Dagnaux, *Chim. Ther.* **7**, 14 (1972).

<sup>156</sup> R. Kimura, T. Yabuuchi, and Y. Tamura, Japanese Patent 7,523 (1961) [*CA* **58**, 13922 (1963)].

<sup>157</sup> R. Kimura, T. Yabuuchi, and Y. Tamura, *Chem. Pharm. Bull.* **8**, 103 (1960).



amine with **99** ( $X = \text{Cl}$ ), obtained directly from **100** ( $X = \text{OH}$ ) by treatment with thionyl chloride.<sup>158</sup>



## V. Spectroscopic Properties

### A. ULTRAVIOLET SPECTRA

Thiophene, simple alkylthiophenes, and halogenothiophenes all have a major absorption ( $\lambda_{\text{max}}$ ) in the region 230–250 nm, with a molar extinction coefficient ( $\epsilon_{\text{max}}$ ) in the range 5200–9000. The parent dithienylmethanes all have a  $\lambda_{\text{max}}$  value very close to those in thiophene and in the methylthiophenes, but with enhanced  $\epsilon_{\text{max}}$  values; however, the  $\epsilon_{\text{max}}$  generally falls short of the sum of those of the two simple constituent thiophene chromophores. Some relevant data are compiled in Table X. The introduction of bromine atoms into the thiophene rings of dithienylmethanes results in a small bathochromic shift, but (with one exception) it makes little difference to the  $\epsilon_{\text{max}}$  value (Table XI). Very little information is available on the UV spectra of other substituted dithienylmethanes.

TABLE X  
UV SPECTRA OF SOME THIOPHENES AND DITHIENYLMETHANES

Compound	Solvent	$\lambda_{\text{max}}$ (nm)	$\epsilon_{\text{max}}$	Ref.
Thiophene	<i>i</i> -C <sub>8</sub> H <sub>17</sub>	231	7,080	159
2-Methylthiophene	<i>i</i> -C <sub>8</sub> H <sub>17</sub>	234	7,590	159
3-Methylthiophene	<i>i</i> -C <sub>8</sub> H <sub>17</sub>	234	5,250	159
2,2'-Dithienylmethane	C <sub>6</sub> H <sub>12</sub>	238	14,180	160
3,3'-Dithienylmethane	C <sub>6</sub> H <sub>12</sub>	237	10,960	2
2,3'-Dithienylmethane	C <sub>6</sub> H <sub>12</sub>	236	13,800	160

<sup>158</sup> I. Yanosuke, K. Masahito, and K. Goro, Japanese Patent 9,986 (1962) [*CA* **59**, 9988 (1963)].

<sup>159</sup> H. D. Hartough, "Thiophene and Derivatives," p. 101. Wiley (Interscience), New York, 1952.

<sup>160</sup> J. M. Barker and R. Smith, unpublished work.

TABLE XI  
 UV SPECTRA OF BROMINATED DITHIENYLMETHANES<sup>a</sup>

Dithienylmethane	Location of bromine	$\lambda_{\max}$ (nm)	$\epsilon_{\max}$
2,2'	3,3'	242	12,900
3,3'	2,2'	242	19,050
	4,4'	246	11,750
	2,4'	241	14,130
2,3'	3	237	10,720
	3,2'	241	12,590
	3,4'	245	10,720

<sup>a</sup> Ref. 2 for cyclohexane solutions [except the first entry (Ref. 3, ethanol)].

The molar extinction coefficients of bis(2-thienyl)alkanes are larger than that of 2,2'-dithienylmethane itself. Some details of UV spectra for compounds **101** are given in Table XII.


 TABLE XII  
 UV SPECTRA OF BIS(2-THIENYL)ALKANES (**101**)

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Solvent	$\lambda_{\max}$ (nm)	$\epsilon_{\max}$	Ref.
H	H	Me	Me	EtOH	235	17,890	36
H	H	Me	Et	EtOH	235	15,540	36
H	H	Et	Et	EtOH	236	19,710	37
H	H	Et	Pr	CHCl <sub>3</sub>	241	14,300	39
H	H	Pr	Pr	EtOH	237	18,800	37
H	H	Bu	Bu	EtOH	237	13,840	37
Me	Me	Me	Me	EtOH	239	15,100	36
Et	H	Et	Pr	EtOH	238	15,600	39
NO <sub>2</sub>	NO <sub>2</sub>	Me	Me	MeOH	328	19,300	89
Et	CHO	Et	Pr	EtOH	249	8,300	39
					301	8,800	
Et	CO <sub>2</sub> H	Et	Pr	EtOH	245	15,000	39
					280	12,500	
MeCO	H	Et	Pr	EtOH	240	10,000	39
					298	12,400	

## B. PROTON MAGNETIC RESONANCE SPECTRA

PMR spectra have been recorded for alkyl-,<sup>4</sup> chloro-,<sup>25,161,162</sup> bromo-,<sup>3,66,161,162</sup> formyl-,<sup>26</sup> acetyl-,<sup>25,161,162</sup> thenoyl-,<sup>26</sup> carboxyl-,<sup>3,26,66</sup> and nitro-substituted<sup>161,162</sup> 2,2'-dithienylmethanes. There is less information about 3,3'-dithienylmethanes. Figures are available for the parent substance,<sup>2</sup> for the 4,4',5,5'-tetramethyl,<sup>79</sup> 3-chloromethyl-2,2',5,5'-tetramethyl,<sup>49</sup> 5,5'-diacetyl,<sup>68</sup> and 2,2', 2,4', and 4,4'-dibromo derivatives,<sup>2</sup> and for the 2,2'-dicarboxylic acid.<sup>2</sup> Reports of PMR spectra in the 2,3'-dithienylmethane series are rarer still. Wynberg and co-workers<sup>2</sup> give data for the 3-bromo, 2,3'-dibromo, and 3,4'-dibromo compounds and for the 2,3'-dicarboxylic acid. 2-Methyl-,<sup>78</sup> 3-formyl-,<sup>77</sup> and 5,5'-diacetyl-2,3'-dithienylmethane<sup>68</sup> have also been studied.

Other compounds for which PMR spectra are recorded include a trimethyl-1,1-bis(2-thienyl)ethane,<sup>4</sup> 2,2-bis(5-nitro-2-thienyl)propane,<sup>89</sup> 2,2-bis(5-formyl- and -5-acetyl-2-thienyl)propane,<sup>26</sup> numerous 2-halogenated 1,1-bis(2-thienyl)alkanes,<sup>25</sup> and some bis(2-thienyl)methanols.<sup>66,79</sup>

These spectra show no remarkable features; the resonance positions and coupling constants are very similar to those in other comparably substituted thiophenes. The following general observations have been made:

1. The protons of the linking methylene group in a number of compounds in the 2,2' and 2,3' series resonate in the region  $\delta$  4.0–4.6; in 3,3'-dithienylmethanes the value is slightly lower ( $\delta$  3.8–4.0).

2. The methylene protons couple weakly ( $J = 0.8$ –1 Hz) with the proton at C-3 when the methylene is at C-2, or with the proton at C-2 when methylene is at C-3.

3. Dithienylalkanes that are unsubstituted elsewhere in the thiophene rings show the typical ABX pattern; the proton at C-5 resonates at the lowest field.

4. The thiophene ring protons have their normal coupling constants, i.e.,  $J_{4-5} = \sim 5.5$  Hz,  $J_{3-4} = \sim 4$  Hz, and  $J_{2-4} = \sim 1.5$  Hz.

## C. MASS SPECTRA

Very little information is available on the mass spectroscopic behavior of dithienylalkanes, but it is clear that an important fragmentation of compounds of the type  $(2-C_4H_3S)_2CHX$  is the loss of X, presumably to produce

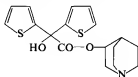
<sup>161</sup> T. Sone and K. Takahashi, *Org. Magn. Reson.* **3**, 527 (1971).

<sup>162</sup> T. Sone, *Nippon Kagaku Zasshi* **86**, 1185 (1965).

a stabilized, benzhydrylic type of species. This behavior has been observed when X has been a methyl,<sup>4</sup> acetyl,<sup>90</sup> and *N,N*-dimethyl<sup>78</sup> group.

#### D. X-RAY CRYSTALLOGRAPHY

An X-ray crystallographic study of 2,2'-dithienylmethane<sup>163</sup> revealed that the two thiophene rings are planar and that the angle between the planes is 87.3°. In the carbinol **102** this angle was found to be 96°.<sup>164</sup>



(102)

<sup>163</sup> R. L. Towns and S. H. Simonsen, *Cryst. Struct. Commun.* **4**, 473 (1975).

<sup>164</sup> A. Meyerhoffer, *Acta Crystallogr.* **26**, 341 (1970).

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# Syntheses of Tetracyclic and Pentacyclic Condensed Thiophene Systems

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## I. Introduction and Scope

This chapter summarizes the syntheses of various tetracyclic and pentacyclic condensed thiophene systems that are reported in *Chemical Abstracts*, *Index of Ring Systems* for the period from 1952 through December 31, 1980 (i.e., through Volume 93). Previous syntheses are reported in the monograph

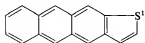
by Hartough and Meisel,<sup>1</sup> to which reference is frequently made. Whenever appropriate, structural assignments from the monograph are revised and information from that volume updated. Some unpublished observations and information from publications that appeared during 1981 are also included. Because the number of tetra- and pentacyclic ring systems bearing one or more thiophene ( $C_4S$ ) rings is very large, additional structural restrictions have been placed on systems selected for inclusion in this chapter. In particular, only compounds composed of one or more  $C_4S$  rings, plus  $C_5$  and/or  $C_6$  rings for the remaining structural units, were chosen. This excludes all systems bearing (a) heteroatoms other than sulfur (b) sulfur heterocyclic units other than  $C_4S$  (e.g.,  $C_3S_2$  and  $C_5S$ ), and (c) carbocyclic rings with fewer than five or more than six members. In every case the completely aromatic (Kekulé) structure is taken as the parent ring system, but information is presented on derived compounds irrespective of the degree of hydrogenation. However, compounds for which the parent system cannot be represented as completely aromatic are excluded. Thus, most steroids (cyclopentadienophenanthrene parent system), many compounds with "extra" hydrogen as revealed in the *Chemical Abstracts* name, spiro compounds, epi compounds, and transannular systems are omitted.

After applying all of the aforementioned restrictions and adding six structures found elsewhere, one obtains the 49 reported tetracyclic and 50 reported pentacyclic condensed thiophene parent systems presented in Tables I and II, respectively. Only 34 of these systems are listed in Hartough and Meisel, but the structures of many of the 34 were highly uncertain in 1952 and parent compounds were rarely known. In this chapter an attempt is made to evaluate critically the reported syntheses of all of these systems and to correlate them into generalized concepts, but principal attention is directed to the post-1952 literature (see Tables III and IV). Interest in polycyclic condensed thiophenes has been expanding, but much confusion remains in structural assignments, and numerous undescribed systems remain to be investigated. One can identify five major areas of activity in the chemistry of condensed thiophenes, listed in approximate chronological order: (a) sulfur dyes; (b) isolation and identification of components from coal tar (now extended to other fossil fuels and to air pollutants); (c) syntheses of compounds for biological testing, especially of carcinogenicity; (d) syntheses of reference compounds for studies of desulfurization and for identification of naturally occurring substances; and (e) studies of physicochemical properties of parent systems per se.

<sup>1</sup> H. D. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), Chaps. 6, 7, Wiley (Interscience), New York, 1954.

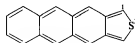
TABLE I  
REPORTED TETRACYCLIC CONDENSED THIOPHENE SYSTEMS<sup>a</sup>

1. Naphthalene thienologs: 2



(1)\*

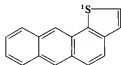
Anthra[2,3-*b*]thiophene  
(refs. 1, 94, 56a)



(2)

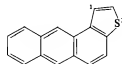
Anthra[2,3-*c*]thiophene  
(refs. 33, 34, 137, 138, 148, 153)

2. Benz[*a*]anthracene thienologs: 10



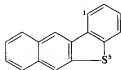
(3)\*

Anthra[1,2-*b*]thiophene  
(refs. 1, 94, 110, 56a)



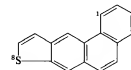
(4)\*

Anthra[2,1-*b*]thiophene  
(refs. 1, 94, 110, 56a)



(5)\*

Benzo[*b*]naphtho[2,3-*d*]thiophene<sup>b</sup>  
(refs. 1, 10, 35, 53, 61, 85, 86, 91, 111, 114, 122, 134, 136, 56a, 106a, 125a)



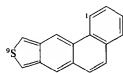
(6)\*

Phenanthro[2,3-*b*]thiophene  
(refs. 1, 66, 123)

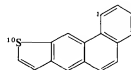
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TABLE I (continued)



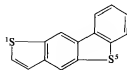
(7)

Phenanthro[2,3-*c*]thiophene<sup>c</sup>

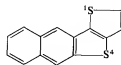
(8)\*

Phenanthro[3,2-*b*]thiophene<sup>c</sup>

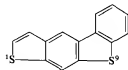
(refs. 1, 66, 123)



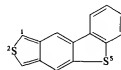
(9)\*

[1]Benzothieno[5,6-*b*][1]benzothiophene  
(ref. 126)

(10)\*

Naphtho[2',3':2,3]thieno[3,2-*b*]thiophene<sup>c</sup>  
(ref. 78)

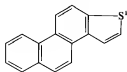
(11)

[1]Benzothieno[6,5-*b*][1]benzothiophene  
(ref. 125)

(12)

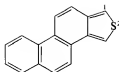
[2]Benzothieno[5,6-*b*][1]benzothiophene  
(ref. 35)

3. Chrysene thienologs: 8



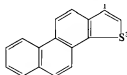
(13)\*

Phenanthro[2,1-*b*]thiophene  
(refs. 1, 47, 66, 144, 159)



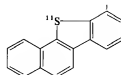
(14)

Phenanthro[1,2-*c*]thiophene  
(ref. 135)



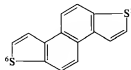
(15)\*

Phenanthro[1,2-*b*]thiophene  
(refs. 66, 77)



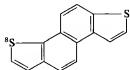
(16)\*

Benzo[*b*]naphtho[2,1-*d*]thiophene  
(refs. 11, 20, 21, 51, 53-55, 86, 87, 91, 101, 103, 134, 141, 157, 56a, 40b)



(17)\*

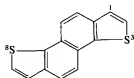
Naphtho[2,1-*b*:6,5-*b'*]dithiophene  
(refs. 1, 159)



(18)

Naphtho[1,2-*b*:6,5-*b'*]dithiophene  
(ref. 1)

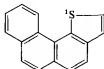
TABLE I (continued)



(19)

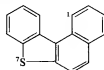
Naphtho[1,2-*b*:5,6-*b'*]dithiophene  
(refs. 1, 63)

4. Benzo[*c*]phenanthrene thienologs: 9



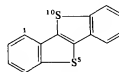
(21)\*

Phenanthro[4,3-*b*]thiophene  
(refs. 1, 66, 77)



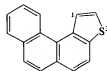
(23)\*

Benzo[*b*]naphtho[1,2-*d*]thiophene<sup>s</sup>  
(refs. 1, 9, 21, 49, 51, 53, 109, 150, 151, 152, 56a)



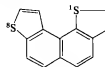
(20)\*

[1]Benzothieno[3,2-*b*][1]benzothiophene  
(refs. 1, 15, 24, 27, 29, 57, 117, 118, 131, 132, 22)



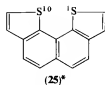
(22)\*

Phenanthro[3,4-*b*]thiophene  
(refs. 1, 66)

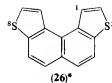


(24)

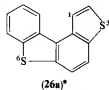
Naphtho[1,2-*b*:7,8-*b'*]dithiophene  
(ref. 1)



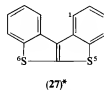
Naphtho[1,2-*b*:8,7-*b'*]dithiophene  
(ref. 129)



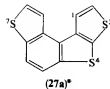
Naphtho[2,1-*b*:7,8-*b'*]dithiophene  
(ref. 64)



[1]Benzothieno[5,4-*b*][1]benzothiophene<sup>a</sup>  
(M. B. Groen, Ph.D. Thesis, Univ. of Groningen,  
Groningen, 1970)



[1]Benzothieno[2,3-*b*][1]benzothiophene  
(refs. 17, 18, 23, 24, 26, 58)



[1]Benzothieno[2,3-*b*:5,4-*b'*]dithiophene<sup>a</sup>  
(ref. 106b)

TABLE I (continued)

## 5. Triphenylene thiologs: 7



(28)\*

Phenanthro[9,10-*b*]thiophene  
(refs. 1, 66, 107)

(29)\*

Phenanthro[9,10-*c*]thiophene  
(refs. 1, 32, 41, 42, 43, 46, 69, 70, 74)

(30)\*

Naphtho[1,2-*b*:3,4-*b'*]dithiophene  
(ref. 63)

(31)\*

Naphtho[1,2-*b*:4,3-*b'*]dithiophene  
(ref. 63)

(32)

Naphtho[1,2-*c*:3,4-*c'*]dithiophene  
(ref. 48)

(33)\*

Benzo[1,2-*b*:3,4-*b'*:5,6-*b''*]trithiophene  
(refs. 76, 162)



(34)\*

Benzo[1,2-*c*:3,4-*c'*:5,6-*c''*]trithiophene  
(refs. 44, 45)

#### 6. Pyrene thienologs: 4



(34a)\*

Phenaleno[1,9-*bc*]thiophene<sup>a</sup>  
(ref. 126a)



(36)

Naphtho[1,8-*bc*:5,4-*b'c'*]dithiophene<sup>a</sup>  
[B. A. Hess and L. J. Schaad  
*J. Am. Chem. Soc.* **95**, 3907 (1973)]



(35)\*

Phenanthro[4,5-*bcd*]thiophene  
(refs. 6, 36, 40a)

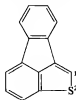


(37)

Naphtho[1,8-*bc*:4,5-*b'c'*]dithiophene<sup>a</sup>  
[B. A. Hess and L. J. Schaad  
*J. Am. Chem. Soc.* **95**, 3907 (1973)]

(continued)

TABLE I (continued)

7. Benzacenaphthene thienologs (one C<sub>5</sub> ring): 6

(38)

Fluoreno[1,9-*bc*]thiophene<sup>a</sup>[M. Scholz and D. Heidrich, *Z. Chem.* 7, 349 (1967)]

(40)\*

Acenaphtho[1,2-*c*]thiophene

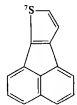
(refs. 1, 32, 33, 71, 72, 73, 79, 155, 72a)



(42)

Acenaphtho[5,4-*b*]thiophene

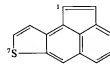
(ref. 77)



(39)\*

Acenaphtho[1,2-*b*]thiophene

(refs. 19, 75, 77)



(41)

Acenaphtho[4,3-*b*]thiophene<sup>a</sup>[H. E. Lumpkin, *Anal. Chem.* 36, 2399 (1964)]

(43)

2,3-Dithiapentaleno[1,6-*ab*]indene<sup>a</sup>(M. Scholz and D. Heidrich, *Z. Chem.* 7, 349 (1967))

8. Compounds with two C<sub>5</sub> rings: 3



(44)

3,6-Dithiacyclopenta[*cd,gh*]pentalene<sup>a</sup>

[B. A. Hess and L. J. Schaad, *J. Am. Chem. Soc.* **95**, 3907 (1973)]



(45)

Pentaleno[1,6-*bc*:4,3-*b'c'*]dithiophene<sup>a</sup>

[B. A. Hess and L. J. Schaad, *J. Am. Chem. Soc.* **95**, 3907 (1973)]



(46)

*as*-Indaceno[4,5-*c*]thiophene  
(ref. 31)

<sup>a</sup> The naming and numbering of each parent system follow current practice by *Chemical Abstracts*. To assist the reader, the number 1 position in the structural formula and the number position of each heterosulfur atom are shown. However, the molecular structure is oriented so as to emphasize the relationship to the structure of its benzolog rather than to conform with the rules of *Chemical Abstracts*. Each system wherein the parent compound has been synthesized and described is designated by an asterisk. Selected data on this parent are presented in Table III. Some key references to the thiophene system are listed in each case.

<sup>b</sup> See text (Section III,A,1) and ref. 10.

<sup>c</sup> Listed in *Chemical Abstracts*, 8th Coll. Index, 22890S (1973), bnt without further reference.

<sup>d</sup> See text (Section III,B,1) and ref. 67.

<sup>e</sup> Not found in *Chemical Abstracts*.

<sup>f</sup> A reported m.p. of 175°C may be erroneous (see ref. 1).

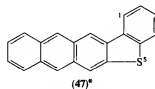
<sup>g</sup> System not yet synthesized; reported only for molecular orbital calculations.

<sup>h</sup> System not yet synthesized; tentatively proposed as a component of coker gas oil.



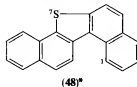
TABLE II  
REPORTED PENTACYCLIC CONDENSED THIOPHENE SYSTEMS<sup>a</sup>

1. Benzonaphthacene thienolog: 1

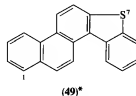


Anthra[2,3-*b*]benzo[*d*]thiophene  
(refs. 1, 81, 89, 90, 119, 142, 161)

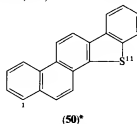
2. Benzochrysene thienologs: 11



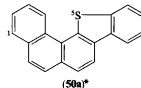
Dinaphtho[1,2-*b*:1',2'-*d*]thiophene  
(refs. 52, 108)



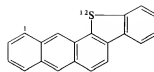
Benzo[*b*]phenanthro[1,2-*d*]thiophene  
(ref. 149)



Benzo[*b*]phenanthro[2,1-*d*]thiophene  
(refs. 93, 102, 129a)

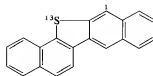


Benzo[*b*]phenanthro[3,4-*d*]thiophene<sup>a,c</sup>  
(ref. 93)



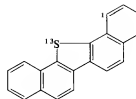
(51)\*

Anthra[1,2-*b*]benzo[*d*]thiophene  
(refs. 102, 103, 139, 140, 142, 157)



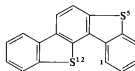
(52)\*

Dinaphtho[1,2-*b*:2',3'-*d*]thiophene  
(refs. 8, 61)



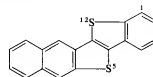
(53)\*

Dinaphtho[1,2-*b*:2',1'-*d*]thiophene<sup>d</sup>  
(refs. 1, 8, 61, 108)



(54)\*

Benzo[1,2-*b*:3,4-*b'*]bis[1]benzothiophene  
(refs. 13, 59, 103, 146)

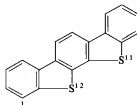


(55)\*

Naphtho[2',3':4,5]thieno[3,2-*b*][1]benzothiophene  
(ref. 100)

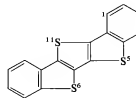
(continued)

TABLE II (continued)



(56)\*

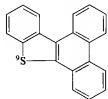
Benzo[2,1-*b*:3,4-*b'*]bis[1]benzothiophene  
(refs. 12, 146)



(57)\*

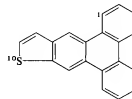
Thieno[3,2-*b*:4,5-*b'*]bis[1]benzothiophene  
(refs. 1, 13, 15)

### 3. Benzotriphenylene thienologs: 2



(58)\*

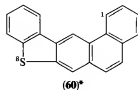
Benzo[*b*]phenanthro[9,10-*d*]thiophene  
(refs. 61, 103, 134)



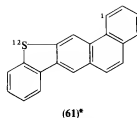
(59)\*

Triphenyleno[2,3-*b*]thiophene  
(ref. 154)

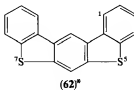
4. Dibenzanthracene thienologs: 4



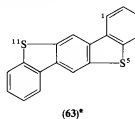
Benzo[*b*]phenanthro[3,2-*d*]thiophene  
(refs. 1, 62, 88, 93)



Benzo[*b*]phenanthro[2,3-*d*]thiophene  
(refs. 1, 62, 88, 93)



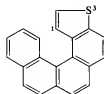
Benzo[1,2-*b*:5,4-*b'*]bis[1]benzothiophene  
(refs. 1, 13, 14, 30, 62, 82, 126)



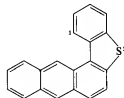
Benzo[1,2-*b*:4,5-*b'*]bis[1]benzothiophene  
(refs. 1, 12, 13, 30, 125, 126)

(continued)

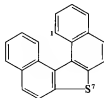
## 5. Dibenzophenanthrene thienologs: 12



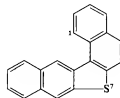
(64)\*

Benzo[5,6]phenanthro[3,4-*b*]thiophene  
(ref. 106b)

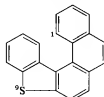
(65)\*

Anthra[2,1-*b*]benzo[*d*]thiophene  
(refs. 110, 119, 120)

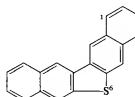
(66)\*

Dinaphtho[2,1-*b*:1',2'-*d*]thiophene<sup>e</sup>  
(refs. 1, 52, 80, 108, 163, 106b)

(67)\*

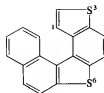
Dinaphtho[2,1-*b*:2',3'-*d*]thiophene  
(refs. 1, 61)

(68)

Benzo[*b*]phenanthro[4,3-*d*]thiophene  
(ref. 1)

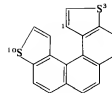
(69)\*

Dinaphtho[2,3-*b*:2',3'-*d*]thiophene  
(refs. 1, 61, 166)



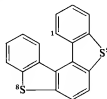
(69a)\*

Naphtho[2,1-*b*]benzo[1,2-*b*:4,3-*b'*]dithiophene<sup>a</sup>  
(ref. 106b)



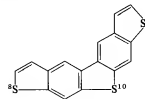
(70)

Phenanthro[3,4-*b*:6,5-*b'*]dithiophene  
(ref. 145)



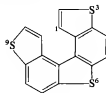
(71)\*

Benzo[1,2-*b*:4,3-*b'*]bis[1]benzothiophene  
(refs. 12, 56, 104)



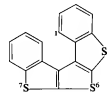
(72)

Thieno[3,2-*f*:4,5-*f'*]bis[1]benzothiophene<sup>f</sup>



(73)

Thieno[3,2-*e*:4,5-*e'*]bis[1]benzothiophene<sup>a</sup>  
(refs. 105, 106c)



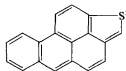
(74)\*

Thieno[2,3-*b*:5,4-*b'*]bis[1]benzothiophene  
(refs. 1, 15)

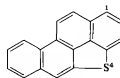
(continued)

TABLE II (continued)

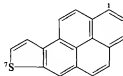
## 6. Benzopyrene thienologs: 7



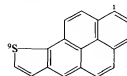
(75)

Benzo[4,5]phenaleno[1,9-*bc*]thiophene  
(ref. 1)

(76)\*

Chryseno[4,5-*bcd*]thiophene  
(ref. 106a)

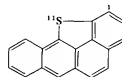
(77)\*

Pyreno[2,1-*b*]thiophene  
(refs. 1, 65a)

(78)\*

Pyreno[1,2-*b*]thiophene  
(ref. 65)

(78a)\*

Pyreno[4,5-*b*]thiophene  
(ref. 65a)

(79)\*

Benzo[2,3]phenanthro[4,5-*bcd*]thiophene  
(ref. 106a)



(80)\*

Triphenyleno[1,12-*bcd*]thiophene  
(ref. 37)

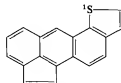
7. Perylene thienolog: 1



(81)\*

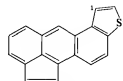
Anthra[1,9-*bc*:5,10-*b'c'*]dithiophene  
(ref. 83)

8. Peri-condensed systems with one C<sub>5</sub> ring: 10



(82)

Aceanthryleno[7,8-*b*]thiophene  
(ref. 99)



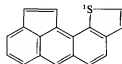
(83)

Aceanthryleno[8,7-*b*]thiophene  
(ref. 99)

(continued)

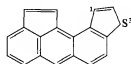


TABLE II (continued)



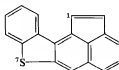
(84)

Aceanthryleno[10,9-*b*]thiophene  
(ref. 99)



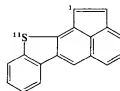
(85)

Aceanthryleno[9,10-*b*]thiophene  
(ref. 99)



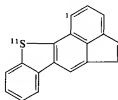
(86)

Acenaphtho[4,3-*b*]benzo[*d*]thiophene  
(ref. 97, 98)



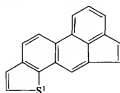
(87)

Acenaphtho[3,4-*b*]benzo[*d*]thiophene  
(refs. 60, 97, 98, 158)



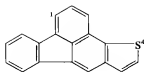
(88)

Acenaphtho[5,4-*b*]benzo[*d*]thiophene  
(refs. 60, 97)



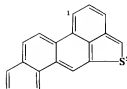
(89)

Acephenanthryleno[7,8-*b*]thiophene  
(ref. 77)



(90)

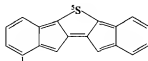
Fluorantheno[3,2-*b*]thiophene<sup>a</sup>  
(ref. 130)



(91)

Cyclopenta[7,8]phenanthro[10,1-*bc*]thiophene<sup>c</sup>

9. Cata-condensed systems with two C<sub>5</sub> rings: 2



(92)

Diindeno[1,2-*b*:2',1'-*d*]thiophene<sup>j</sup>  
(ref. 1)



(93)

Diindeno[2,1-*b*:1',2'-*d*]thiophene<sup>k</sup>  
(refs. 1, 127)

<sup>a</sup> See footnote *a*, Table I. However, selected data on parent compounds are presented in Table IV.

<sup>b</sup> Not found in *Chemical Abstracts*.

<sup>c</sup> Since physical properties of the parent molecule have not yet been reported, only a brief entry for this system is given in Table IV.

<sup>d</sup> The m.p. of 147°C reported by Henriques (ref. 163) may be erroneous (see Section III,D).

<sup>e</sup> See text (Section III,D) and ref. 165.

<sup>f</sup> This appears to be an erroneous entry in *Chemical Abstracts* [93, 141266 (1980)]. The correct structure is 73.

<sup>g</sup> See text (Section III,C,2) and ref. 106c.

<sup>h</sup> Reported only as a dimer.

<sup>i</sup> Known only as a steroid derivative [*Chemical Abstracts*, 9th Coll Index, 12979CS (1978)]

<sup>j</sup> Structure uncertain.

<sup>k</sup> See text (Section III,C,3,d).

TABLE III  
SELECTED LITERATURE DATA FOR PARENT AROMATIC TETRACYCLIC CONDENSED THIOPHENES<sup>a</sup>

Cmpd. no. <sup>b</sup>	Synthetic method <sup>c</sup>	Starting material <sup>d</sup>	No. of steps	Overall yield (%)	m.p. (°C)	Physical appearance	Spectral data <sup>e</sup>	Derivatives <sup>f</sup> (m.p. °C)	References <sup>g</sup>
1	C,3,c	358a	3	51	320 dec.	Yellow needles	UV, P		94, 56a
3	C,4,b	3-VinylTh + 399	4	14	120	Leaflets	UV, PMR, M	TNP(145), TNF(227)	94, 56a
4	C,4,b	2-VinylTh + 399	4	7	196	Yellow leaflets	UV, PMR, M, F	TNP(157), TNF(231)	94, 56a
5	C,3,a	See Scheme 21	5	15	161	Weakly fluorescent	UV, PMR, IR, MS, F, P	Q(215), SO <sub>2</sub> (268)	11, 53, 86, 111, A, B
6	C,3,c	356	3	56	161.5	Plates	UV, PMR, M	Q(165.5)	66, 123
8	C,3,c	2-Li-354 + Np-1-CHO	6	11	122	Fine plates	UV, PMR, M	Q(201)	66, 123
9	C,3,c	(2-BTh)CH <sub>2</sub> (3-Th)	1	25	130				126
10	B,2	See Scheme 11	5	<sup>a</sup>	169	Yellow plates		TNP(131), TNF(226)	78
13	C,2	288 + Np-1-CHO	2	75	238	Fine plates	UV, PMR, M		66
15	C,2	<sup>a</sup>	2	24	170	Fine plates	UV, PMR, M	2-Me-15(143)	66, 77
16	C,2	3-Styryl-BTh	1	72	186	Fine plates	UV, PMR, IR, MS	TNP(145), SO <sub>2</sub> (234)	11, 53, 56a, C, D
17	B,1	Np-2,6-dithiol	2	9	265	Lustrous flakes	UV	TNB(201)	E
20	A,2	PhCHCl <sub>2</sub>	1	61	215.5		UV, M, F, L	SO <sub>2</sub> (269), di-SO <sub>2</sub> (338)	25, 131, F
21	C,2	<sup>i</sup>	2	12	95	Plates	UV, PMR, M	TNP(173.5), TNF(224.5)	66, 77

22	C,2	288 + Np-2-CHO	2	68	83.5		UV, PMR, M		66
23	B,1	PhSH + 176	3	25	104	Long needles	UV, MS	TNP(149), SO <sub>2</sub> (229)	51, 53, 56a C
25	C,3,d	See Scheme 30	4	20	126	Plates	UV, PMR, M	364(118)	129
26	B,1	200	2	22	163	Plates	MS	TNP(185)	64, C
26a	C,2	288 + BTh-2-CHO	2	48	150		UV, PMR		104, G
27	A,2	114	1	54	142	Monoclinic	PMR, X	SO <sub>2</sub> (235), di-SO <sub>2</sub> (315)	17, 18, 23
27a	C,2	j	2	40	172.5		UV, PMR, MS		106b
28	B,1	203	2	25	153	Needles	UV, PMR, M		66, 107
29	A,4	149-9,10-(CH <sub>2</sub> X) <sub>2</sub>	2	13 <sup>k</sup>	169	Felted needles	UV, PMR	29-1,3-di-CO <sub>2</sub> H(270 dec.)	43, 68
30	B,1	196	2	70 <sup>f</sup>	134		UV	TNP(185), TNB(208)	63
31	B,1	See Scheme 6	2	6	169	Needles	UV, PMR	TNP(182)	56, 63
33	D	485 (R = H)	2	"	161		UV	486, R = H(184)	162
34	A,4	155	2	36	238		UV, PMR, CMR	TCNE, DDQ, TCNQ <sup>g</sup>	45
34a	C,3,c <sup>e</sup>	See Scheme 28a	4	6	156	Prisms	UV, PMR, IR, MS	TNP (195 dec.)	126a
35	A,3	149	3	25	135 <sup>p</sup>	Prisms <sup>p</sup>	UV, PMR, IR, MS	SO(202), SO <sub>2</sub> (273)	6, 36
39	B,2	215	4	48	67	Yellow needles	UV, PMR	8-Cl-39(115), 8-Br-39(138)	75, H
40	B,2	208	3	"	98.5		UV, PMR	210(360)	71, 72, 79, H

(continued)

TABLE III (continued)

- <sup>a</sup> When a choice of methods is available, the simplest, highest-yielding, or most explicitly described procedure has been entered.
- <sup>b</sup> See Table I for structural formula and name.
- <sup>c</sup> The letters and numbers indicate the subsection of Section III in which the synthesis is discussed.
- <sup>d</sup> Abbreviations: Th, thienyl; BTh, benzo[*b*]thienyl; Np, naphthyl; Ph, phenyl.
- <sup>e</sup> Abbreviations: UV, ultraviolet; PMR, proton magnetic resonance; CMR, <sup>13</sup>C magnetic resonance; IR, infrared; MS, mass spectrum; F, fluorescence; L, luminescence of crystals; M, molecular ion in MS; P, phosphorescence; X, X-ray crystallography.
- <sup>f</sup> Abbreviations: TNP, 2,4,6-trinitrophenol (picric acid) complex; TNB, 1,3,5-trinitrobenzene complex; TNF, 2,4,7-trinitro-9-fluorenone complex; Q, quinone of compound; SO, *S*-oxide (sulfoxide); SO<sub>2</sub>, *S,S*-dioxide (sulfone); TCNE, tetracyanoethylene complex; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone complex; TCNQ, tetracyanoquinone dimethane complex.
- <sup>g</sup> Overall yield, 48% for first three steps. Yields on other steps not reported.
- <sup>h</sup> Diethyl 3-thenylphosphonate + Np-1-CHO.
- <sup>i</sup> Diethyl 3-thenylphosphonate + Np-2-CHO.
- <sup>j</sup> Thieno[2,3-*b*]thiophene-2-carboxaldehyde + 2-ThCH<sub>2</sub>PPh<sub>3</sub>Cl.
- <sup>k</sup> This yield probably could be increased by dehydrogenation of the dihydro-**29** also formed.
- <sup>l</sup> Crude yield.
- <sup>m</sup> Yield, 40–50% for first step; yield for second step not reported.
- <sup>n</sup> Complexes were not fully described.
- <sup>o</sup> Modified Bradsher reaction.
- <sup>p</sup> Also needles, m.p. 140°C.
- <sup>q</sup> Yield, 59% for the first two steps; yield not reported for third step (decarboxylation).
- <sup>r</sup> Numbered references are text footnotes, lettered references are as follows: (A) A. N. Nikitina *et al.*, *Khim. Geterot. sikl. Soedin.* 7 925 (1972); (B) R. N. Akhobadze *et al.*, *Soobsh. Akad. Nauk Gruz. SSR* 77, 369 (1975); 78, 365 (1975); R. N. Akhobadze *et al.*, *Izv. Akad. Nauk SSSR, Ser. Fiz.* 39, 2390 (1975) [*CA* 83 8640, 87899 (1975); 84 67166 (1976)]; (C) "American Petroleum Institute, Research Project 44, Catalog of Mass Spectra." Nos. 1376, 1309, 1415, 1406, 1416, 1500, and 1499; (D) F. R. McDonald and G. L. Cook, *U.S. Bur. Mines Rep. Inves. No.* 6911 (1967); (E) B. D. Tilak, *Proc. Indian Acad. Sci.* 33A, 71 (1951); (F) Yu. M. Vinetskaya *et al.*, *Khim. Geterotsikl. Soedin.* 4, 180 (1968); (G) M. B. Groen, Ph.D. Thesis, University of Groningen, 1970; (H) K. D. Bartle *et al.*, *J. Chem. Soc. (B)* 2092, (1971).

TABLE IV  
SELECTED LITERATURE DATA FOR PARENT AROMATIC PENTACYCLIC CONDENSED THIOPHENES<sup>a</sup>

Cmpd. no. <sup>b</sup>	Synthetic method <sup>c</sup>	Starting material <sup>d</sup>	No. of steps	Overall yield (%)	m.p. (°C)	Physical appearance	Spectral data <sup>e</sup>	Derivatives <sup>f</sup> (m.p., °C)	References <sup>g</sup>
47	C,3,b	2-Br-BTh + 327	3	8	288 <sup>h</sup>	Fluorescent yellow plates <sup>h</sup>	UV, F	325(311), 324(287)	89, 90, A, B
	C,1	249	1	i	250	Orange-red crystals			
48	B,1	168	3	76 <sup>j</sup>	164	Plates	IR, MS, P	TNP(162)	52, C, D, E
49	C,4,c	410 + 431	3	55	169	Yellow needles		SO <sub>2</sub> (278)	149
50	C,2	BTh-2-CHO <sup>k</sup>	3	5	331		PMR	5-OH-50(ca. 250), 5-OCH <sub>3</sub> -50(163)	102, 129a
50a	C,1	243	1	i	i				93
51	C,4,a	394 (R = H)	4	13	227	Cream plates	PMR	Q(274), TNB(180)	102, 103, 157
52	B,1	168	3	8	317	Fluorescent flakes	UV	TNF(231)	8, 61
53	B,3	1-Br-Np	2	15	253	Fluorescent plates	UV, P	TNF(257)	8, 61, 108, D
54	C,4,a	394 (R = H) + 410	3	47	168	Fluffy needles	UV, PMR, MS	TNB(175), di- SO <sub>2</sub> (> 360)	13, 56, 59, 103, C
55	C,1	i	2	1	287	Yellow leaflets	UV, PMR, MS	Q(410), 7-Me- 55(186)	100
56	C,4,a	108	2	≥ 20	270	Flakes		TNB(193)	12, 146
57	A,1	108	1	16	303 <sup>m</sup>	Silvery flakes		TNP, TNB do not form	13
58	B,1	182	3	26	142	Fluorescent needles		TNP(174), TNF(216)	61
59	C,5	see Scheme 36	2	16	178		UV, PMR, IR, MS	Q(231), SO <sub>2</sub> (259)	154
60	C,1	243 <sup>n</sup>	1	54	142	Leaflets	UV	di-TNP(177), Q(261) <sup>p</sup>	88, 93
	C,3,b	see Scheme 26	2	5	115	Yellow needles		Mono-TNP(169)	62

(continued)

TABLE IV (continued)

Cmpd. no. <sup>b</sup>	Synthetic method <sup>c</sup>	Starting material <sup>d</sup>	No. of steps	Overall yield (%)	m.p. (°C)	Physical appearance	Spectral data <sup>e</sup>	Derivatives <sup>f</sup> (m.p., °C)	References <sup>g</sup>
61	C,1	<sup>p</sup>	2	26	323	Needles or flakes	UV	Q(256) <sup>g</sup> ; TNP, TNB do not form	62, 88, 93
62	C,3,c	BTh	2	45	220	Lustrous flakes		105(315), di-TNP(182)	13, 126
63	A,1	103	1	2	315	Lustrous flakes		348(307); 6,12-diMe-63(265)	12, 125
64	C,2	Th-2-CHO	2	50	139.5		UV, MS		106b
65	C,4,a	393 + 399 see also p. 202	2	<sup>i</sup>	<sup>i</sup>		UV, F	323(279), 6-Ph-323(226)	90, 110, A
66	B,1	176 + 171a	3	78 <sup>j</sup>	207	Cream flakes	UV, PMR, MS, P		52, 106b, C, D, F
67	B,1	188 + 171a	3	<sup>k</sup>	197	Plates		TNF(154)	61
69	D	492	1	15	254	Yellow plates	IR	TNF(225)	61, G
69a	C,2	<sup>r</sup>	2	44	160		MS		106b
71	C,2	see Scheme 18	2	48	185	Needles	UV, PMR	di-TNP(118)	12, 56, 104, H
74	A,2	113	1	20	183 <sup>m</sup>	Yellow needles			15
76	C,3,c	see Scheme 28a	4	18	173	Needles	UV, IR, PMR, MS		106a, F
77	C,3,c	see Scheme 28a	4	9	157	Yellow Leaflets	UV, IR, PMR, MS	TNP(198)	65a
78	B,1	1-Br-pyrene	3	0.4	146	Yellow flakes	UV	TNP(183)	65
78a	B,1	4-Br-pyrene	2	5	185	Yellow crystals	UV, IR, PMR, MS		65a
79	C,3,c	see Scheme 28a	4	27	153	Yellow needles	UV, IR, PMR, MS		106a, F
80	A,3	150	1	18	191	Fine needles	UV, PMR, MS	SO(225), SO <sub>2</sub> (327)	37
81	B,3	see Eq. (5)	2	43	260	Thin yellow flakes	UV, PMR, F, MS, ESR <sup>a</sup>	I <sub>2</sub> , SbF <sub>5</sub> complexes <sup>f</sup>	83

<sup>a</sup> See footnote *a*, Table III.

<sup>b</sup> See Table II for structural formula and name.

<sup>c</sup> See footnote *c*, Table III.

<sup>d</sup> See footnote *d*, Table III.

<sup>e</sup> See footnote *e*, Table III.

<sup>f</sup> See footnote *f*, Table III.

<sup>g</sup> Yield, 38% for first step; yields for other steps not reported.

<sup>h</sup> Variations are reported in melting points and colors of products formed.

<sup>i</sup> Not reported.

<sup>j</sup> Crude yield.

<sup>k</sup> See Scheme 17 and **285**

<sup>l</sup> Thieno[3,2-*b*][1]benzothiophene.

<sup>m</sup> Structure **57** or **74** was proposed for a compound of m.p. 190–193°C formed from reaction of benzo[*b*]thiophene with sulfur (ref. 1).

<sup>n</sup> See Scheme 16.

<sup>o</sup> It is reported (ref. 1) that condensation of benzo[*b*]thiophenedicarboxylic anhydride with naphthalene gives two isomeric quinones melting at 157° and 257°C, respectively. It was proposed that they have the structures **245** and **247**, expected for quinones of **60** and **61**, respectively.

<sup>p</sup> Benzo[*b*]thiophene + 1-methyl-2-naphthoic acid.

<sup>q</sup> Yield, 17% for two steps; yield not reported for Tilak annulation step per se.

<sup>r</sup> 2-Thenyltriphenylphosphonium bromide + naphtho[2,1-*b*]thiophene-2-carboxaldehyde.

<sup>s</sup> ESR, electron spin resonance of radical-cation.

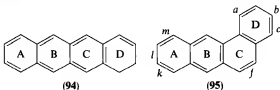
<sup>t</sup> Not completely identified.

<sup>u</sup> Numbered references are text footnotes, lettered references are as follows: (A) A. N. Nikitina *et al.*, *Khim. Geterotsikl. Soedin.* **7**, 925 (1972); (B) L. F. Utkina *et al.*, *Soobsch Akad. Nauk Gruz SSR* **82**, 373 (1976) [*CA* **85** 169057 (1976)]; (C) "American Petroleum Institute, Research Project 44, Catalog of Mass Spectra," Nos. 1376, 1309, 1415, **1406**, 1416, 1500, and 1499; (D) M. Zander *Z. Naturforsch.* **31A**, 677 (1976); (E) F. R. McDonald and G. L. Cook *U.S. Bur. Mines Rep. Invest. No.* 6911 (1967); (F) R. Depaus, *J. Chromatogr.* **176**, 337 (1979); W. Karcher *et al.*, in "Polynuclear Aromatic Hydrocarbons" (P. W. Jones and P. Leber, eds.) p. 341. Ann Arbor Science Publishers, Ann Arbor (1979); (G) M. P. Groenewege, *Spectrochim. Acta* **11**, 579 (1958); (H) M. P. Groen and H. Wynberg, *J. Am. Chem. Soc.* **93**, 2968 (1971).



## II. Thienologs and Benzologs

The close physicochemical analogies between the benzene and thiophene rings have been noted repeatedly.<sup>2</sup> Compounds wherein a  $-\text{CH}=\text{CH}-$  portion of a benzene ring is replaced by a sulfur atom, or vice versa for a thiophene ring, are called "isosteres" to indicate that the benzene and thiophene rings effectively occupy the same geometry in space.<sup>3</sup> In this chapter the terms "benzolog" and "thienolog," rather than "isostere," are used to denote compounds which bear that same structural relationship. Thus, in Table I, anthrathiophenes **1** and **2** are thienologs of the linearly condensed hydrocarbon (benzolog) naphthacene (**94**), and anthrathiophenes **3** and **4** are thienologs of the angularly condensed benzolog benz[*a*]anthracene (**95**).

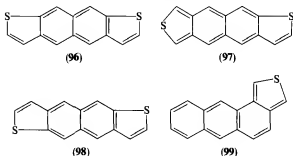


There are many advantages of using the thienolog correlation. Perhaps most important is that one can use the structural formulas of the known and predicted polycyclic aromatic hydrocarbons as a point of reference for writing the structures of all of the more numerous condensed thiophenes that are theoretically possible. For example, compounds **1** and **2** are the only possible monothienologs of **94**, but there are also three possible unknown dithienologs (**96–98**) of **94** wherein both A and D rings are heterocyclic. Clearly, one cannot write structures for thienologs of **94** in which a B or C ring is heterocyclic or for ones with more than two heterosulfur atoms. Similarly, compound **95** leads to seven monothienologs (**3–8**, **99**) by simple replacement of the variously lettered  $-\text{CH}=\text{CH}-$  portions of **95** (and its Kekulé resonance contributing forms) by  $-\text{S}-$ . Also, one predicts a total of 15 dithienologs of **95** (three for sulfur atoms in rings C and D; nine for A and D; and three for A and C), as well as nine trithienologs of this hydrocarbon. The replacement method works well for all of the six possible tetracyclic and 15 possible pentacyclic aromatic hydrocarbons bearing only  $\text{C}_6$  units.<sup>4</sup> It is easily extended to aromatic hydrocarbons

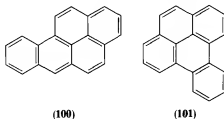
<sup>2</sup> G. M. Badger, "The Chemistry of Heterocyclic Compounds," p. 147. Academic Press, New York, 1961.

<sup>3</sup> A. Burger, W. B. Wartman, and R. E. Lutz, *J. Am. Chem. Soc.* **60**, 2628 (1938); H. Erlenmeyer, E. Berger, and M. Leo, *Helv. Chim. Acta* **16**, 733 (1933).

<sup>4</sup> For a list of these benzologs see A. Pullman and B. Pullman, in "Advances in Cancer Research" (J. P. Greenstein and A. Haddow, eds.), Vol. 3, p. 130. Academic Press, New York, 1955.



bearing one or more  $C_5$  units by effecting replacement only in the  $C_6$  rings (see parts 7 and 8, Table I; parts 8 and 9, Table II). For simplicity and correlation of structures, 14 of the aforementioned pentacyclic benzologs are categorized in Table II as benzo derivatives of the six tetracyclic benzologs in Table I (see parts 1–6 in both tables). Perylene, the other pentacyclic benzolog (see part 7, Table II), does not fit into a category. It might be noted, for example, that compounds **75–78** and **79** are thienologs of the carcinogen benzo[*a*]pyrene (**100**), whereas compounds **78a** and **80** are thienologs of the noncarcinogen benzo[*e*]pyrene (**101**).<sup>5</sup>



It is apparent from the tables that numerous possible condensed thiophenes of four- or five-membered rings have not yet been described in the literature. Under each formula in the tables is given the *Chemical Abstracts* name of the compound, which should be used in searching for literature abstracted after 1980.

### III. Synthetic Methodology

Most commonly, tetracyclic and pentacyclic condensed thiophenes are synthesized by the process of annulation, i.e., by constructing one or more rings onto a precursor molecule by an intermolecular or intramolecular

<sup>5</sup> See ref. 4, pp. 123–124 for carcinogenic activities of benzopyrenes.

process. Thus, most of the following synthetic methodologies are categorized first in terms of the nature of the ring produced, whether a sulfur heterocyclic ring or a carbocyclic one, and second in terms of the reagents or type of reaction used. In sulfur-bridging methods (Section III,A) the heterosulfur ring is produced by direct insertion of an inorganic sulfur atom into an organic precursor. Thiannulation (Section III,B) effects formation of the heterosulfur ring from an organosulfur precursor wherein the sulfur atom is part of an open-chain structure. In homoannulation (Section III,C) a carbocyclic ring is produced in a compound that already bears an intact heterosulfur ring.

A few synthetic methods that do not fit neatly into one of the annulation categories are compiled in Section III,D. These methods include ring contraction by extrusion of one sulfur atom from a disulfide bridge and molecular rearrangement of a preformed polycyclic condensed thiophene substrate. However, many molecular rearrangements accompany annulation processes per se or subsequent work-up of the products, and these are discussed as part of the annulation scheme itself. A small number of reactions are intentionally cited out of order for the sake of discussion. These reactions are cross-referenced in the text to aid the reader in locating them. Compounds derived through substitution into a preformed parent aromatic system are generally omitted from this chapter.

## A. SULFUR BRIDGING

The direct insertion of a sulfur atom into the skeleton of a precursor molecule to form a heterocyclic ring is known as sulfur bridging. The heterosulfur atom regularly arises from elemental sulfur or an inorganic sulfur compound such as  $\text{H}_2\text{S}$ ,  $\text{Na}_2\text{S}$ ,  $\text{SO}_2$ , or  $\text{SOCl}_2$ . Sulfur bridging may involve simple addition, addition-elimination, or replacement of an atom, ion, or molecule.

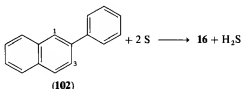
### 1. *Method a: Use of $\text{S}_8$ , $\text{AlCl}_3$ , and Heat*

Although method *a* works well for the conversion of biphenyl to dibenzothiophene, it has generally given poor yields (if any) of the desired bridged products with other substrates.<sup>6,7</sup> Notable examples of substrates that produced no isolable bridged product are phenanthrene,<sup>7</sup> 2,2'-binaph-

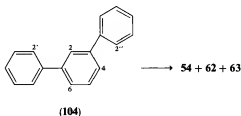
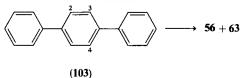
<sup>6</sup> L. H. Klemm, D. R. McCoy, and D. R. Olson, *J. Heterocycl. Chem.* **7**, 1347 (1970).

<sup>7</sup> L. H. Klemm, J. J. Karchesy, and D. R. McCoy, *Phosphorus Sulfur* **7**, 9 (1979).

thyl,<sup>8</sup> and 1-phenylnaphthalene.<sup>9</sup> However, a small yield of **16**, not **5** as proposed by the authors,<sup>10</sup> resulted from bridging into the 1-position (not the 3-position) of 2-phenylnaphthalene (**102**) at 110°–200°C.<sup>11</sup> Tilak and co-workers prepared a series of doubly and triply bridged compounds from



terphenyls, phenylbenzo[*b*]thiophenes, and bisbenzo[*b*]thiophenes. Some of the bridged products resulted from skeletal rearrangement of the starting material through the influence of the  $\text{AlCl}_3$ . *p*-Terphenyl (**103**) produced the two expected pentacyclic condensed thiophenes **56** (3%, from bridgings at C-2 and C-3 to the adjacent ring) and **63** (2%, from bridgings at C-2



and C-4).<sup>12</sup> *m*-Terphenyl (**104**) formed **54** (3%, from 2,2'- and 2'',4-bridgings), **62** (3%, from 2',6- and 2'',4-bridgings), and **63** (1%, after rearrangement plus bridgings).<sup>13</sup> For structure proof **62** was oxidized to the quinone **105** (m.p. 312°C).<sup>14</sup> 3-Phenylbenzo[*b*]thiophene (**106**) was rearranged to **107**,

<sup>8</sup> W. L. F. Armarego, *J. Chem. Soc.*, 433 (1960).

<sup>9</sup> W. Davies, N. W. Gamble, and W. E. Savage, *J. Chem. Soc.*, 4678 (1952).

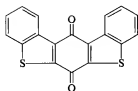
<sup>10</sup> O. Kruber and L. Rappen, *Ber.* **73**, 1184 (1940).

<sup>11</sup> L. H. Klemm, J. J. Karchesy, and R. F. Lawrence, *J. Heterocycl. Chem.* **15**, 773 (1978).

<sup>12</sup> D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res.* **17B**, 260 (1958).

<sup>13</sup> L. J. Pandya, G. N. Pillai, and B. D. Tilak, *J. Sci. Ind. Res.* **18b**, 198 (1959).

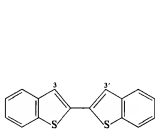
<sup>14</sup> F. Mayer, A. Mombour, W. Lassman, W. Werner, P. Landmann, and E. Schneider, *Justus Liebigs Ann. Chem.* **488**, 259 (1931).



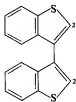
(105)

(106)  $R^1 = H$ ;  $R^2 = C_6H_5$ (107)  $R^1 = C_6H_5$ ;  $R^2 = H$ 

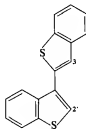
which bridged at C-3 to form **20** (5%).<sup>15</sup> Compound **108** underwent 3,3'-bridging to give the expected **57** (16%), the structure of which was established by Raney nickel desulfurization to 1,4-diphenylbutane.<sup>13</sup> However, both **109** and **110** gave two bridged products, **57** and an incompletely characterized isomer (m.p. 190°C, expected to be **111** but assigned the alternative structure **112**).<sup>15</sup>



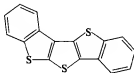
(108)



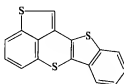
(109)



(110)



(111)



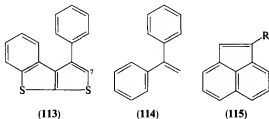
(112)

## 2. Method b: Use of $S_8$ and Heat

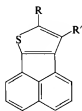
In contrast to method *a*, method *b* appears to be free of the problem of skeletal rearrangement, but the substrate must be more reactive than biphenyl in order for bridging to occur.<sup>6</sup> Success has been achieved with alkylarenes and arylalkenes ( $H_2S$  is evolved), but dimerization frequently occurs. Structures of various reported products remain to be elucidated.<sup>6,7</sup> For example,

<sup>15</sup> T. S. Murthy, L. J. Pandya, and B. D. Tilak, *J. Sci. Ind. Res.* **20B**, 169 (1961).

toluene and sulfur yield both **107** and an incompletely identified product,  $C_{14}H_8S_2$  (m.p.  $209^\circ C$ ), which may be **20**.<sup>6,16</sup> Medium yields of products were reported from bridging of **113** at C-7 to give **74** (20%),<sup>15</sup> of **108** across the 3,3'-positions to form **57** (51%), and from double bridging of 1,1-diphenylethene (**114**) to yield **27** (25–54%)<sup>17</sup> via the intermediate **106** (20%).<sup>15</sup> The structure of **27** was established by means of X-ray crystallography.<sup>18</sup>



1-Alkylacenaphthylenes (**115**), in which R is ethyl, *n*-propyl, or isopropyl, likewise give both dehydrogenation and bridging products on treatment with sulfur at  $185^\circ C$ ; the parent compound acenaphtho[1,2-*b*]thiophene **39**, its 8-methyl (**116**, R =  $CH_3$ ; R' = H; m.p.  $61.5^\circ C$ ) and 9-methyl derivative (**116**, R = H; R' =  $CH_3$ ; m.p.  $127^\circ C$ ) are formed, respectively, in yields of 15%.<sup>19</sup> The methyl products were characterized by the formation of acetoxymercuri and benzoyl derivatives, wherein substitution was believed to occur in the thiophene ring. The structure of the 8-methyl-9-benzoyl derivative was verified by chromic acid oxidation to naphthalene-1,8-dicarboxylic anhydride.



(116) (**39** if R = R' = H)

An interesting extension of method *b* by Nasipuri *et al.*<sup>20</sup> involved heating **117** with excess sulfur at  $250^\circ$ – $270^\circ C$  to give both dehydrogenation and

<sup>16</sup> A. W. Horton, *J. Org. Chem.* **14**, 761 (1949).

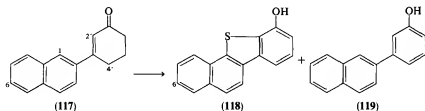
<sup>17</sup> S. Dayagi, I. Goldberg, and U. Shmueli, *Tetrahedron* **26**, 411 (1970).

<sup>18</sup> I. Goldberg and U. Shmueli, *Acta Crystallogr.* **B27**, 2164 (1971).

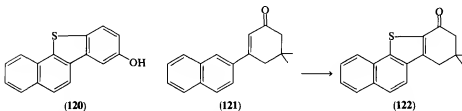
<sup>19</sup> J. Morel and Y. Mollier, *C. R. Hebd. Seances. Acad. Sci.* **260**, 5300 (1965).

<sup>20</sup> D. Nasipuri, I. D. Dalal, and S. K. Ghosh, *Synthesis*, 59 (1977).

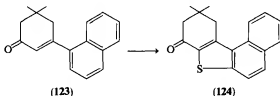
bridging reactions, which produced a mixture of **118** (24%, m.p., UV, IR, PMR) and **119** (50%). The 6-methoxy derivative of **117** reacted analogously



(10% of bridged product). Surprisingly, when a small amount of  $I_2$  was added to the reaction mixture, **117** underwent 1,4'-bridging instead of 1,2'-bridging to yield **120** (33%). Dehydrogenation of **117** cannot proceed to completion before bridging is initiated since 3-arylphenols do not bridge under the reaction conditions. Dehydrogenation of the keto ring was circumvented in starting materials **121** and **123**, which produce bridged compounds



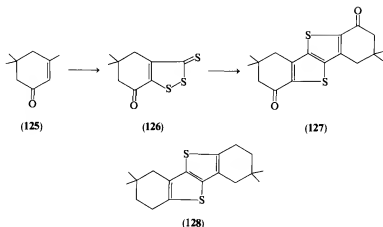
**122** (40%) and **124** (35%), respectively.<sup>21</sup> Addition of  $I_2$  to the reaction mixtures in these cases, however, gave only tars. Somewhat analogously,



Ebel *et al.*<sup>22</sup> treated isophorone (**125**) with sulfur at 210°–250°C to give bridged product **126**, an isomer of **126** and the dimer **127** (20%, m.p. 312°C dec.).<sup>22</sup> Compound **126** also slowly produced **127** on heating. Wolff-Kishner reduction of **127** gave **128** (22%, m.p. 244°C).

<sup>21</sup> D. Nasipuri, A. Sarkar, P. K. Chakraborty, and I. D. Dalal, *J. Indian Chem. Soc.* **55**, 1232 (1978).

<sup>22</sup> M. Ebel, L. Legrand, and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 161 (1963).



Medium yields (38–61%) of bridged products are obtained when polyhaloalkyl- and polyhaloalkenylbenzenes ( $X = \text{Cl}$  or  $\text{Br}$ ) are heated with sulfur, sometimes in refluxing 1,2-dichlorobenzene at  $250^\circ \pm 30^\circ\text{C}$ . Under these conditions halogen atoms on alkyl, alkenyl, and thiophene rings (but generally not on benzene rings) are eliminated as  $\text{HX}$  or  $\text{S}_2\text{X}_2$  and are replaced by one or more sulfur bridges to the benzene ring(s). Dimerization or even polymerization may occur. These dehalocycloaddition reactions were investigated simultaneously by Geering in the United States and by Voronkov and Udre in Russia. The latter workers are primarily responsible for the reaction pathways shown in Schemes 1<sup>23,24</sup> and 2.<sup>24–26</sup> For  $\text{R} = \text{H}$  the final product **132** is the same as **27**, which is also formed when the tribromo analog of **129** is used. Compound **130** ( $\text{R} = \text{H}$ ), used as a starting material, gave **27** in 54% yield,<sup>23</sup> whereas **131** ( $\text{R} = \text{Cl}$ ) was isolated as an intermediate (40%) when the reaction temperature was kept low ( $200^\circ\text{--}240^\circ\text{C}$ ). Compound **27** also resulted from 1,1,1,2-tetrachloro-2,2-diphenylethane (41%). The conversion **130**  $\rightarrow$  **132** was successful for  $\text{R} = \text{OCH}_3$  (product m.p.  $181^\circ\text{C}$ ) and probably for  $\text{R} = \text{CH}_3$ , but not for  $\text{R} = \text{Cl}$ , which yielded two unidentified products ( $\text{C}_{14}\text{H}_7\text{Cl}_3\text{S}$ , m.p.  $121^\circ\text{C}$ ;  $\text{C}_{14}\text{H}_6\text{Cl}_2\text{S}$ , m.p.  $270^\circ\text{C}$ ).<sup>24</sup> For the transformation of **129** to **132** products of m.p.  $268^\circ\text{C}$

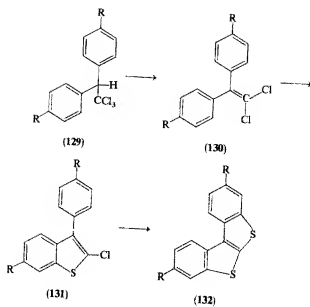
<sup>23</sup> M. G. Voronkov and V. E. Udre, *Khim. Geterotsikl. Soedin.* **4**, 43 (1968); M. G. Voronkov and V. Udre, U.S.S.R. Patent 199,909 (1967) [*CA* **68**, 114580 (1968)].

<sup>24</sup> E. J. Geering, U.S. Patent 3,278,552 (1966) [*CA* **66**, 10920 (1967)].

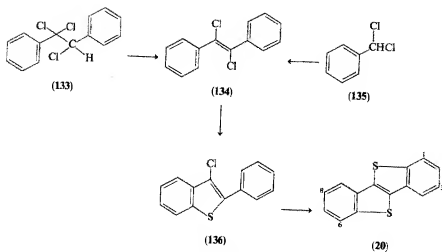
<sup>25</sup> M. G. Voronkov and V. E. Udre, *Khim. Geterotsikl. Soedin.* **1**, 683 (1965); *Khim. Seraorg. Soedin. Soderzh. Neftiyakh Nefteprod.* **9**, 233 (1972) [*CA* **79**, 125981 (1973)]; *Khim. Geterotsikl. Soedin.*, *Akad. Nauk Latv. SSSR*, **148**, 683 (1965) [*CA* **63**, 5581 (1965); **64**, 11148 (1966)].

<sup>26</sup> M. G. Voronkov and V. E. Udre, *Khim. Geterotsikl. Soedin.* **6**, 457 (1970).





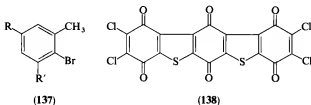
SCHEME 1



SCHEME 2

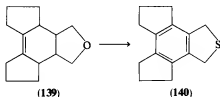
for  $R = Cl$  and  $284^\circ C$  for  $R = Br$  were obtained.<sup>23</sup> In the synthesis of **20**, one can use **133**, **134** (51%), **135**, **136**, 1,1,2,2-tetrachloro-1,2-diphenylethane (50%), benzal bromide (8%), or even 1-chloro-2-trichloromethylbenzene.<sup>27</sup> Geering<sup>24</sup> claims that benzotrichloride gives **20**, but the Russians found this substrate to be unreactive.<sup>25</sup> The structure of **20** is clearly distinguished from that of **27** by means of dipole moment measurements;  $\mu = 0$  for **20** and 1.11 D for **27**.<sup>28</sup>

Low yields (1–9%) of **20** and its methyl derivatives result from cyclo-dimerization of **137**.<sup>29</sup> For  $R = CH_3$ ,  $R' = H$  one obtains the 3,8-dimethyl



derivative (m.p.  $242^\circ C$ ) and, for  $R = R' = CH_3$ , the 1,3,6,8-tetramethyl derivative (m.p.  $231.5^\circ C$ ) of **20** (UV, IR, PMR, and MS data for both). Heating chloranil with sulfur at  $295^\circ C$  gave linear polymerization with attendant sulfur bridging to yield trimer **138** (0.8%) plus the corresponding dimer (10%) and tetramer (0.1%).<sup>30</sup>

There are three reported processes in which another heteroatom (O, Rh, or Ir) in a five-membered ring is replaced by sulfur. Along with dehydrogenation of **139** by means of sulfur was the formation of **140** (25%, m.p.  $112^\circ C$ )



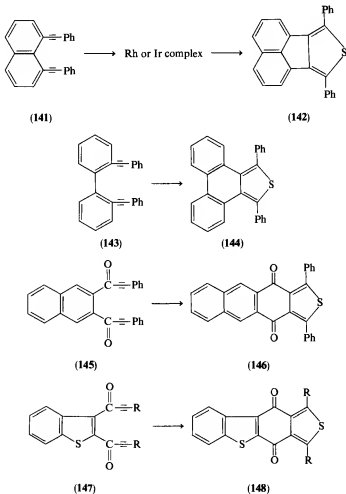
<sup>27</sup> E. J. Geering, U.S. Patent 3,433,874 (1969) [CA 71, 38940 (1969)].

<sup>28</sup> M. G. Grunfest, Yu. Kolodyazhnyi, V. E. Udre, M. G. Voronkov, and O. A. Osipov, *Khim. Geterotsikl. Soedin.* 6, 448 (1970).

<sup>29</sup> M. G. Voronkov and L. N. Khokhlova, *Zh. Org. Khim.* 10, 811 (1974); M. G. Voronkov and V. E. Udre, *Khim. Geterotsikl. Soedin.* 2, 527 (1966); M. G. Voronkov and A. N. Pereferkovich, *Angew. Chem., Int. Ed. Engl.* 8, 272 (1969).

<sup>30</sup> G. Beck, H. Holschmidt, and K. Ley, German Patent 2,224,836 (1973) [CA 80, 47965 (1974)].

as a by-product.<sup>31</sup> Treatment of the diynes **141** and **143** with tris(triphenylphosphine)rhodium(I) chloride gave Rh complexes, which were converted to the diphenyl derivatives **142** (53%, m.p. 205°C) and **144** (60%, m.p. 206°C) on reaction with sulfur in benzene at 20°C.<sup>32</sup> The conversion **141** → **142** was also effected in comparable yield via an Ir complex formed with tris(triphenylphosphine)iridium(I) chloride.<sup>33</sup> The bisynones **145** and **147** (R = Ph



<sup>31</sup> G. LeGuillanton, *Bull. Soc. Chim. Fr.*, 1702 (1966).

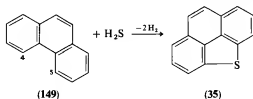
<sup>32</sup> E. Müller, R. Thomas, M. Sauerbier, E. Langer, and D. Streichfusz, *Tetrahedron Lett.*, 521 (1971).

<sup>33</sup> E. Müller and C. Beissner, *Chem. Ztg., Chem. App.* **96**, 170 (1972) [*CA* **76**, 140997 (1972)].

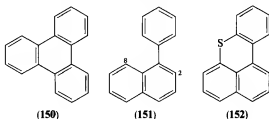
or  $C_2H_3$ ) were converted, respectively, to quinones **146** and **148** in a similar manner, but at  $140^\circ C$ .<sup>33-35</sup>

### 3. Method c: Use of $H_2S$ and a Catalyst

This method has been developed largely by Klemm *et al.* and is discussed in a recent review,<sup>7</sup> which gives details on catalysts, procedure, and possible mechanisms. Examples include formation of the peri-condensed compounds **35** (29–39%), from bridging at positions 4 and 5 of the phenanthrene molecule **149** at ca.  $630^\circ C$  in the presence of various sulfided mixed metallic oxide catalysts,<sup>6,36</sup> and **80** (18%), from similar bridging in the triphenylene molecule **150** at  $500^\circ C$ .<sup>37</sup> Since the sulfur bridge forms by substitution at the sterically most hindered positions of these hydrocarbon substrates, method



c is particularly attractive and useful as a synthetic pathway to peri-condensed thiophenes. 2-Phenylnaphthalene (**102**) gives preferential bridging at C-1 of the naphthalene ring to form **16** (24%) plus a small amount (1%) of **5** from



bridging at C-3.<sup>11</sup> 1-Phenylnaphthalene (**151**) yields a mixture of products, which varies in composition with reaction temperature.<sup>38</sup> Expected are **23**, from bridging at C-2, and the benzothiaxanthene **152**,<sup>39,40</sup> from bridging at

<sup>34</sup> E. Mueller, H. Muhm, and E. Langer, *Chem. Ztg., Chem. App.* **95**, 525 (1971) [*CA* **75**, 76456 (1971)].

<sup>35</sup> E. Müller, E. Luppold, and W. Winter, *Chem. Ber.* **108**, 237 (1975).

<sup>36</sup> L. H. Klemm and W. Hsin, *J. Heterocycl. Chem.* **13**, 1245 (1976).

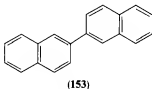
<sup>37</sup> L. H. Klemm and R. F. Lawrence, *J. Heterocycl. Chem.* **16**, 599 (1979).

<sup>38</sup> L. H. Klemm and Sovitj Pou, unpublished results.

<sup>39</sup> W. Davies, F. C. James, S. Middleton, and Q. N. Porter, *J. Chem. Soc.*, 1565 (1955).

<sup>40</sup> W. Davies, Q. N. Porter, and J. R. Wilmshurst, *J. Chem. Soc.*, 3366 (1957).

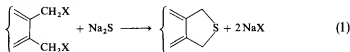
C-8. Only **23** has been isolated. 2,2'-Binaphthyl (**153**) undergoes reaction, but the product(s) have not yet been identified.<sup>38</sup>



Method *c* offers a simple pathway to condensed thiophenes that may simulate the natural geochemical formation of these compounds in fossil fuels.<sup>7</sup> However, separation of the bridged product(s) from the accompanying starting material is experimentally difficult. The peri-condensed compounds **35** and **80** can be isolated via their sulfoxides (formed *in situ* in the reaction mixtures) by means of column chromatography on silica gel.<sup>36,37</sup> Preliminary studies indicate that it may be possible to separate directly on a column of silica gel impregnated with a polynitro aromatic complexing agent,<sup>40a</sup> whereas it should be easy to isolate the sulfur-bridged biaryl **16** on alumina.<sup>40b</sup>

#### 4. Method *d*: Use of $\text{Na}_2\text{S}$ and a Solvent

Several research groups have constructed [*c*]-fused dihydrothiophene rings onto aromatic hydrocarbon nuclei, as shown in Eq. (1), where  $\text{X} = \text{Br}$  or  $\text{Cl}$ . From 9,10-bis(halomethyl)phenanthrene at refluxing temperature in



ethanol or dioxane were obtained **154** and/or its aromatized system phenanthro[9,10-*c*]thiophene (**29**).<sup>41-43</sup> Millar and Wilson<sup>41</sup> reported a melting point of 205°C (crude) for **154**, whereas Stille and Foster<sup>42</sup> obtained a value of 166°C (40%). Shields *et al.*<sup>43</sup> found that their crude product could be chromatographically separated into **154** (10%, needles, m.p. 181°C) and **29** (13%, needles, m.p. 169°C). Also reported were the sulfoxide (needles, m.p. 216°C)<sup>43</sup> and the sulfone (m.p. 260° ± 10°C) of **154**.<sup>41,42</sup> Similarly, two groups of workers converted **155** to **156** (80–90% crude; 40% pure, m.p.

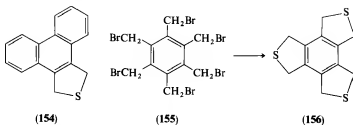
<sup>40a</sup> L. H. Klemm and John Jordan, unpublished results.

<sup>40b</sup> L. H. Klemm, F. H. W. Lee, and R. F. Lawrence, *J. Heterocycl. Chem.* **16**, 73 (1979).

<sup>41</sup> I. T. Millar and K. V. Wilson, *Proc. Chem. Soc.*, 217 (1963); *J. Chem. Soc.*, 2121 (1964).

<sup>42</sup> J. K. Stille and R. T. Foster, *J. Org. Chem.* **28**, 2708 (1963).

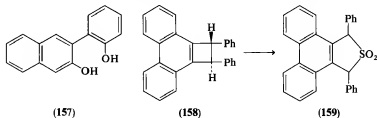
<sup>43</sup> J. E. Shields, D. E. Remy, and J. Bornstein, *J. Org. Chem.* **40**, 477 (1975).



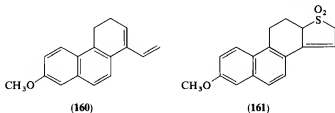
246°C; PMR singlet at  $\delta$  4.18) and then to the trisulfone (m.p. > 350°C; PMR singlet at  $\delta$  4.44).<sup>44,45</sup> Dehydrogenation of **156** with DDQ in refluxing chlorobenzene gave the parent tetracycle **34** (45%).<sup>45</sup>

### 5. Methods e: Miscellaneous Procedures

Other reported bridging reactions are the conversion of the diphenolic compound **157** to **5** (6%) by heating with  $P_2S_5$ ,<sup>10</sup> the insertion of  $SO_2$  into **158** at 150°C to give **159** (49%, m.p. > 320°C),<sup>46</sup> the addition of  $SO_2$  to **160**



in a solvent at room temperature to give **161** (60%),<sup>47</sup> the double addition of  $SO_2$  to **162** at room temperature to produce the disulfone **163** (m.p. > 300°C),<sup>48</sup> the reaction of **164** with  $SOCl_2$  in refluxing  $CCl_4$  to yield (after



<sup>44</sup> L. G. Harruff, M. Brown, and V. Boekelheide, *J. Am. Chem. Soc.* **100**, 2893 (1978).

<sup>45</sup> H. Hart and M. Sasaoka, *J. Am. Chem. Soc.* **100**, 4326 (1978).

<sup>46</sup> M. P. Cava and D. Mangold, *Tetrahedron Lett.*, 1751 (1964).

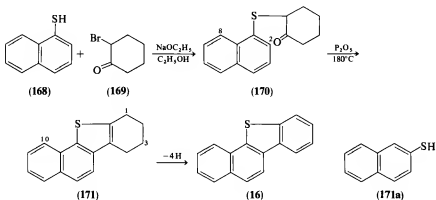
<sup>47</sup> D. L. Quin and N. Rao, *Phosphorus Sulfur* **5**, 371 (1979).

<sup>48</sup> H. Hart, A. Teuerstein, M. Jeffares, W.-J. H. Kung, and D. L. Ward, *J. Org. Chem.* **45**, 3731 (1980).

<sup>50</sup> L. A. Walter, W. K. Chang, J. Kenney, and I. Douvan, *J. Med. Chem.* **17**, 459 (1974). See also H-W. Voigtländer and E. Graf., *Justus Liebig's Ann. Chem.* **625**, 196 (1959).

1. *Method a: Tilak Thiannulation*

In 1951–1953 Rabindran and Tilak<sup>51,52</sup> introduced a new “dibenzo-thiophene synthesis” and extended it to tetracyclic and pentacyclic systems. This method involves a two-step process of condensing a thioarenol with an  $\alpha$ -halo ketone or  $\alpha$ -haloacetal to form an  $\alpha$ -(arylthio) ketone or  $\alpha$ -(arylthio)-acetal intermediate, which is subsequently cyclized intramolecularly. The three principal variations introduced by Tilak and co-workers are presented in Schemes 3, 5, and 6 and were summarized in 1960.<sup>52a</sup>



SCHEME 3

Scheme 3 illustrates the use of an  $\alpha$ -halocyclohexanone to add two condensed rings (including the thiophene one) to the starting arenethiol molecule. The intermediate **170** (87%) cyclized to **171** (70%, m.p.  $98^\circ\text{C}$ ).<sup>51</sup> Dehydrogenation to **16** is usually accomplished by heating with Se<sup>51</sup> (90%) or Pd–C (80%),<sup>53</sup> but the procedure is troublesome and not always reliable. In the case of the 10-chloro derivative of **171** (prepared from 8-chloronaphthalene-1-thiol) dehydrogenation with Se was accompanied by loss of Cl.<sup>54</sup> However, the use of *N*-bromosuccinimide and benzoyl peroxide in refluxing  $\text{CCl}_4$ , instead of Se, gave dehydrogenation with retention of the Cl substituent to yield **172** (68%, m.p.  $148^\circ\text{C}$ ).<sup>54</sup> To show that Se dehydrogenation

<sup>51</sup> K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci.* **37A**, 564 (1953), and references cited therein.

<sup>52</sup> K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci.* **38A**, 271 (1953).

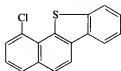
<sup>52a</sup> B. D. Tilak, *Tetrahedron* **9**, 76 (1960).

<sup>53</sup> E. Campaigne and S. W. Osborn, *J. Heterocycl. Chem.* **5**, 655 (1968). See also E. B. McCall, British Patent 701,267 (1953) [*CA* **49**, 4027 (1955)].

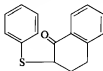
<sup>54</sup> K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci.* **37A**, 557 (1953).



of **171** had not caused a structural rearrangement, Rabindran and Tilak<sup>51</sup> effected hydrodechlorination of **172** to **16** with  $\text{Cu}_2\text{O}$ ,  $\text{Ac}_2\text{O}$ , and pyridine (69% yield). The formation of **172**, moreover, corroborated the fact that **170**

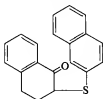


(172)

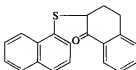


(173)

cyclizes at C-2 of the naphthalene ring rather than at C-8 to produce, after dehydrogenation, the benzothioxanthene **152**. Raney nickel desulfurization of **16** yielded 2-phenylnaphthalene (**102**). Campbell and Keen<sup>55</sup> extended the Tilak procedure to obtain the 1-methyl (m.p.  $164^\circ\text{C}$ ) and 3-methyl (m.p.  $186^\circ\text{C}$ ) derivatives of **16**. Analogous routes produced **23** (36–82%) from **173**,<sup>51,53</sup> **66** (78%) from **174**, and **48** (83%) from **175**.<sup>52</sup> Bromo ketone **176** was a precursor in these cases. It adds three rings, including the thiophene one, on cyclization. A question of the structure of **23** was raised by Tilak and Rabindran.<sup>51</sup> Although Raney nickel desulfurization of **23** produced the expected 1-phenylnaphthalene (**151**), the UV absorption spectrum of **23**<sup>53</sup> showed "greater similarity" to that of chrysene than to that of its benzolog, benzo[*c*]phenanthrene.<sup>51</sup> However, Gogte presented PMR data and arguments to support the structural assignment of **23**.<sup>56</sup> Also, total syntheses of the three possible naphthobenzothiophenes and their sulfones by Campaigne and Osborn<sup>53</sup> differentiate clearly among these isomers and confirm the Tilak and Rabindran assignments, including that for the conversion of **171a** to **23** (76%) by the method of Scheme 3<sup>51</sup> (cf. Ref. 56a).



(174)



(175)



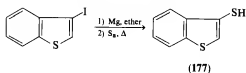
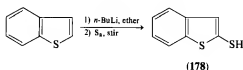
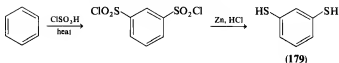
(176)

In modifications of Scheme 3 it was necessary to synthesize the thiol and/or halo ketone precursors in many instances. Some typical pathways to unusual thiols are shown in Scheme 4.

<sup>55</sup> A. D. Campbell and A. R. Keen, *J. Chem. Soc.*, 1637 (1964).

<sup>56</sup> V. N. Gogte, *Indian J. Chem.* **9**, 312 (1971).

<sup>56a</sup> Y. Tominaga, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.* **18**, 967 (1981).

(a) Grignard synthesis<sup>57</sup>(b) Organolithium intermediate<sup>58</sup>(c) Reduction of a sulfonyl chloride<sup>59</sup>

SCHEME 4

Other starting materials prepared for adaptations of Scheme 3 are **180**–**188**. Products reported are **189** (m.p. 165°C) from **180** and **187**,<sup>60</sup> **190** (m.p. 145.5°C) from **181** and **187**,<sup>60</sup> **20** (desulfurized to 1,2-diphenylethane) from **177** and **169**,<sup>57</sup> **27** (41% overall) from **178** and **169**,<sup>58</sup> **54** (14% overall) from double cyclization at C-2 and C-4 of **179** with **169** (1:2 molar ratio),<sup>59</sup> **58** (26% overall) from **182** and **187** (dehydrogenation by means of sulfur),<sup>61</sup> and a separable mixture of **63** (11% overall) from double cyclization at C-2 and C-5 of **183** and **71** (15% overall) from double cyclization at C-2 and C-3 of **183** with **169** (1:2 molar ratio).<sup>12</sup> The structure of **63** was established by Tilak reaction of **184** with 2 equivalents of **169** to form the intermediate **191** (43%, m.p. 278°C), which converted to **63** (44%) on heating with Se.<sup>12</sup> The structure of **71** was corroborated by its PMR spectrum.<sup>56</sup> Tilak reaction of **185** with 2 equivalents of **169** gave the intermediate **192** (X = Cl; 46%, m.p. 140°C), which was hydrodechlorinated (by means of Cu<sub>2</sub>O, Ac<sub>2</sub>O, and pyridine) to **192** (X = H; 86%, m.p. 137°C) and then dehydrogenated to **54** (67%)<sup>59</sup> as a structure proof for **54**. Similarly, reaction of **186** and **169** formed

<sup>57</sup> V. V. Ghaisas and B. D. Tilak, *J. Sci. Ind. Res.* **16B**, 345 (1957).

<sup>58</sup> R. B. Mitra, L. J. Pandya, and B. D. Tilak, *J. Sci. Ind. Res.* **16B**, 348 (1957).

<sup>59</sup> D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res.* **13B**, 829 (1954).

<sup>60</sup> P. Faller and P. Cagniant, *Bull. Soc. Chim. Fr.*, 2985 (1968).

<sup>61</sup> R. Wilputte and R. H. Martin, *Bull. Soc. Chim. Belg.* **65**, 874 (1956).



(180) X = SH; Y = H

(181) X = H; Y = SH



(182)



(183)



(184)



(185)



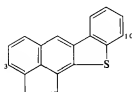
(186)



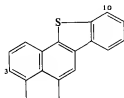
(187)



(188)

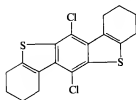


(189)

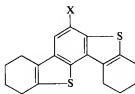


(190)

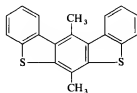
**193** (69%, m.p. 189°C; sulfone m.p. > 360°C).<sup>62</sup> Chloro ketone **188** was reacted with (a) benzenethiol to produce the condensed tetracycle **5** (3%



(191)



(192)

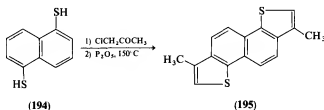


(193)

<sup>62</sup> G. N. Pillai, T. S. Murthy, and B. D. Tilak, *Indian J. Chem.* **1**, 112 (1963).

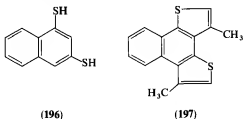
overall), (b) 1-naphthalenethiol (**168**) to give **52** (8% overall), and (c) 2-naphthalenethiol (**171a**) to form **67**.<sup>61</sup> Raney nickel desulfurizations converted these three products to the expected biaryls. The use of **188** in Tilak reactions eliminated the difficulty encountered with 3-chloro-2-tetralone, which undergoes dehydrochlorination to yield 2-naphthol in the base-catalyzed condensation with thiols.<sup>61</sup>

Scheme 5 illustrates Tilak thiannulation by means of an acyclic  $\alpha$ -halo ketone. This variation leads to an alkyl-substituted, terminally condensed thiophene ring. The cyclization of **194** to **195** (m.p. 271.5°C; UV similar to that of chrysene) was effected in only 14% yield.<sup>63</sup> In the only other use of



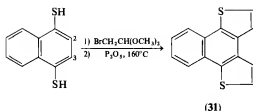
SCHEME 5

this general procedure, dithiol **196** was condensed with  $\alpha$ -chloroacetone and then cyclized to **197** (18% overall; m.p. 165°C).<sup>63</sup>



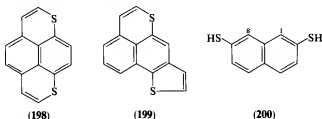
The third method of Tilak thiannulation uses bromoacetaldehyde dimethylacetal (or its equivalent) to condense with an arenethiol. The formation of a terminal thiophene ring is shown in Scheme 6, where cyclizations take place at C-2 and C-3 (6% overall).<sup>63</sup> Two alternative structures, **198** and **199**, were considered for the product of cyclization. These were rejected in favor of **31** on the basis of the lack of color in the purified product, the orange color of its picrate, the close similarity of its UV spectrum to that of triphenylene, and its PMR spectrum.<sup>56,63</sup> In an analogous reaction **196** was converted to **30** (overall yield 70% crude).<sup>63</sup> Compound **30** also showed the

<sup>63</sup> H. S. Desai and B. D. Tilak, *J. Sci. Ind. Res.* **20B**, 22 (1961).

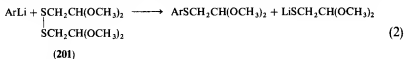


SCHEME 6

first three structural criteria found for **31** and, in addition, formed 1,3-diethylnaphthalene on desulfurization. Dithiol **200** was also doubly cyclized (at C-1 and C-8) to yield **26**, which was purified via the picrate (22% overall).<sup>64</sup>



In one modification of Scheme 6 the intermediate aryl  $\omega$ -dimethoxyethyl sulfide was synthesized from an aryllithium and 2,2,2',2'-tetramethoxydiethyl disulfide (**201**, Eq. 2).<sup>65</sup> The lithium salt by-product can be recycled to **201** by aeration. Of interest is the formation of the pentacycle **78** on



cyclization of **202**<sup>65</sup> (0.4% overall for three steps from 1-bromopyrene, precursor of 1-pyrenyllithium). Again, the white color of the product and its UV absorption spectrum were cited as evidence that cyclization had occurred at C-2 rather than at C-10. Analogously, 4-bromopyrene yielded **78a** (5%).<sup>65a</sup> Castle and co-workers reacted the Grignard reagent from **203** with **201** and cyclized the intermediate at C-10 to produce **28** (25% overall).<sup>66</sup> Tilak reported the cyclization of **204** to a phenanthrothiophene (30%, m.p.

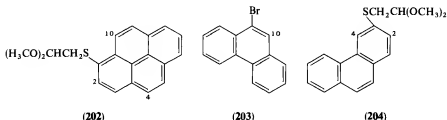
<sup>64</sup> V. V. Ghaisas, K. Rabindran, and B. D. Tilak, *Proc. Indian Acad. Sci.* **37A**, 114 (1953); K. Rabindran and A. V. Sunthakar, *Bombay Technologist* **2**, 84 (1952) [*CA* **48**, 10725 (1954)].

<sup>65</sup> L. J. Pandya and B. D. Tilak, *J. Sci. Ind. Res.* **18B**, 371 (1959); *Chem. Ind.*, 981 (1958).

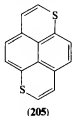
<sup>65a</sup> R. Pratap, Y. Tominaga, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.* **18**, 973 (1981).

<sup>66</sup> M. Iwao, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.* **17**, 1259 (1980).

82°C)<sup>1,67</sup> and made the reasonable assumption that cyclization had occurred at C-2 to give **8**. However, Castle and co-workers, who have prepared samples of all possible phenanthro[*b*]thiophenes, offer strong evidence that Tilak's cyclization actually took place at C-4 to form **22**.<sup>66</sup>



It is evident that Tilak thiannulation is a convenient pathway to condensed thiophenes, although overall yields vary from minute to good. While structural rearrangements have not been encountered, one must be aware of the possible formation of condensed thiapyran products in place of condensed thiophenes, especially in the variation illustrated by Scheme 6. As an example, **194** yielded **205** as the only cyclization product.<sup>67a</sup>



## 2. Method b: Base-Catalyzed Thiannulation

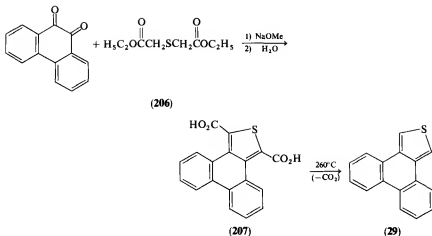
The Hinsberg reaction has been used in two cases to prepare tetracyclic condensed thiophenes from 1,2-diketones and thiodiglycolic esters.<sup>68</sup> One example is shown in Scheme 7 for the synthesis of **29** (13% overall).<sup>43,69</sup> If water is not added during the process, one isolates the half-ester (27% for methyl half-ester of **207**), which undergoes decarboxylation with copper

<sup>67</sup> B. D. Tilak, *Proc. Indian Acad. Sci.* 33A, 85 (1951).

<sup>67a</sup> It should be noted that J. E. Banfield, W. Davies, B. C. Ennis, S. Middleton, and Q. N. Porter [*J. Chem. Soc.*, 2603 (1956)] questioned structure **205**, but their doubts (although pertinent) apparently were incorrect.

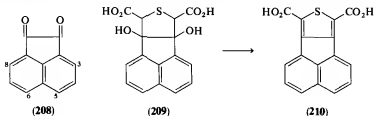
<sup>68</sup> O. Hinsberg, *Ber.* 43, 901 (1910).

<sup>69</sup> R. O. Kochkanyan, S. N. Baranov, and G. I. Belova, U.S.S.R. Patent 425,909 (1974) [*CA* 81, 49559 (1974)].



SCHEME 7

bronze at  $300^\circ\text{C}$  to give the 1-carbomethoxy derivative of **29** (71%).<sup>70</sup> In the other case acenaphthenequinone (**208**) was condensed with **206** to give a dihydroxydicarboxylic acid (**209**) (77%, m.p.  $252^\circ\text{C}$ ), easily dehydrated to **210** (m.p.  $360^\circ\text{C}$ ) by means of boiling  $\text{Ac}_2\text{O}$ , boiling  $\text{Ac}_2\text{O}$ -pyridine (76% yield), or concentrated  $\text{H}_2\text{SO}_4$  at  $40^\circ\text{--}50^\circ\text{C}$  (62% yield).<sup>71,72</sup> The diethyl ester of **209** is also dehydrated by  $\text{Ac}_2\text{O}$ , and treatment of **209** with  $\text{SOCl}_2$  in DMF gives the diacid chloride of **210**.<sup>72a</sup> Isolation of **209** rather than the



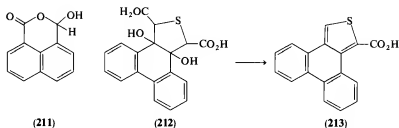
expected **210** is ascribed to the presence of strain in the thiophene ring of the latter. The stereochemistry of **209** is believed to be all *cis*. The half-ester of **209** (68%) can also be prepared directly. A by-product (up to 10%) of the condensation is **211**. Various substituted acenaphthenequinones have been

<sup>70</sup> D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J. C. S. Perkin I*, 2079 (1972).

<sup>71</sup> A. Birch and D. A. Crombie, *Chem. Ind.*, 177 (1971).

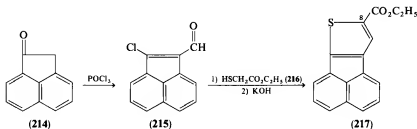
<sup>72</sup> V. I. Koshelev and V. L. Plakidin, *Zh. Org. Khim.* **9**, 597 (1973). For additional derivatives of **209** see V. I. Koshelev and V. L. Plakidin, *Zh. Vses. Khim. Obshchest.* **19**, 358 (1974) [*CA* **81**, 91285 (1974)].

<sup>72a</sup> See also O. Dann, K.-J. Bamberg, and H. Sucker, *Pharmazie* **23**, 135 (1968).



investigated as starting materials in the Hinsberg reaction.<sup>72,73</sup> The 3-methoxy derivative of **208** gave its derivative **209** (45%); the 3,8-dimethoxy derivative did not react; the 5,6-dinitro derivative yielded a mixture of products wherein only a trace of the **209** compound could be detected by IR spectrum; the 5-chloro derivative reacted faster than **208** itself (82% yield of **209** derivative); and the 5,6-dichloro derivative formed the **209** compound (28%) plus the dichloro derivative of **211** (60%). Substituted diacid chlorides of **210** were also obtained from the three substituted **209** compounds. On the basis of their experience with the **209** series, Koshelev and Plakidin<sup>74</sup> treated 9,10-phenanthrenequinone with **206** in a mixture of KOH and methanol to give a colorless product, believed to be the intermediate **212** (80% as monohydrate) on the basis of IR and PMR spectra and its decomposition to **213** (m.p. 164.5°C) at 127°C. Decarboxylation of **210** occurred with Cu in boiling quinoline to give the parent compound (**40**).<sup>71</sup>

A second method of base-catalyzed thiannulation is illustrated in Scheme 8. The reaction proper involves a 1-chloro-2-formylalkene (such as **215**; normally prepared from **214** by the Vilsmeier-Haack reaction) and thio-glycolic ester (**216**). Ester **217** (75% from **215**) was hydrolyzed to the carboxylic acid (74%) and decarboxylated to the parent tetracycle (**39**) (87%).<sup>75</sup> Other



SCHEME 8

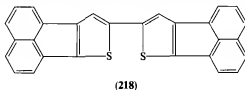
<sup>73</sup> V. L. Plakidin, V. I. Koshelev, and N. N. Ivarovskaya, *Zh. Org. Khim.* **9**, 1490 (1973).

<sup>74</sup> V. I. Koshelev and V. L. Plakidin, *Zh. Org. Khim.* **10**, 1340 (1974).

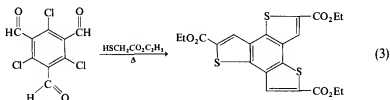
<sup>75</sup> S. Hauptmann, M. Scholz, H.-J. Köhler, and H.-J. Hofmann, *J. prakt. Chem.* **311**, 614 (1969); S. Hauptmann, M. Weiszenfels, M. Scholz, E.-M. Werner, H.-J. Köhler, and J. Weisflog, *Tetrahedron Lett.*, 1317 (1968).



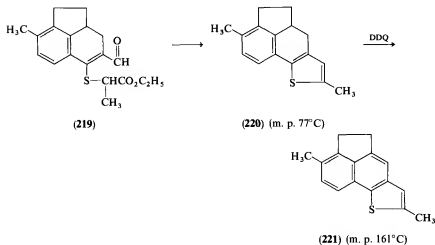
derivatives of **39** that are prepared from **217** are the 8-CH<sub>2</sub>OH (95%), the 8-carboxamide (95% for two steps), the 8-CN (62% for three steps), the 8-formyl (86% for two steps), the biaryl **218** (27% from treatment of **217** with



LiAlH<sub>4</sub> in refluxing THF), and a monobromo derivative of **217**.<sup>75</sup> Roos and Wagner claim the conversion shown in Eq. (3).<sup>76</sup>



In a modification of Scheme 8 Cagniant and Kirsch<sup>77</sup> treated analogs of **215** first with Na<sub>2</sub>S in DMF and then with ethyl bromoacetate or ethyl  $\alpha$ -bromopropionate to isolate the intermediate ester aldehyde of type **219**,

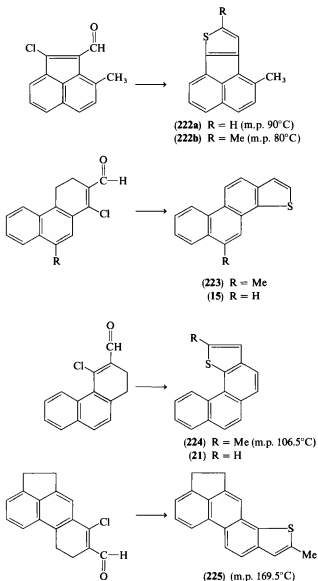


SCHEME 9

<sup>76</sup> E. Roos and K. Wagner, German Patent 1,902,050 (1970) [*CA* 73, 87909 (1970)].

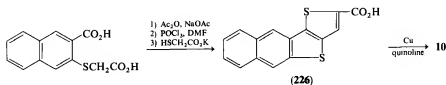
<sup>77</sup> P. Cagniant and G. Kirsch, *C. R. Hebd. Seances Acad. Sci.* **281C**, 393 (1975).

subsequently cyclized (50% average overall yield) and (where appropriate) also aromatized by means of DDQ. Typical isolated intermediates are shown in Scheme 9, and other overall transformations are presented in Scheme 10. Compound **223** is described only as the dihydro derivative. The method of



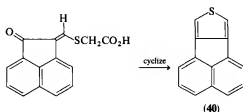
SCHEME 10

decarboxylation was not indicated. Another modified route by Cagniant *et al.*<sup>78</sup> is shown in Scheme 11, where thioglycolic acid (rather than its ester) is used and a preceding base-catalyzed intramolecular thiannulation is illustrated. Compound **226** melts at 250°C dec.



SCHEME 11

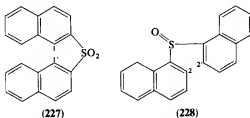
Hauptmann *et al.*<sup>79</sup> have claimed the synthesis of **40** (26% for two steps) by Scheme 12.



SCHEME 12

### 3. Methods c: Intramolecular Thiannulations

Gogte *et al.*<sup>80</sup> and Wilputte and Martin<sup>61</sup> employed base-catalyzed intramolecular thiannulations, which have been little used despite their simplicity. Treatment of the lithium derivative of sulfone **227** with anhydrous  $\text{CuCl}_2$  effected 1,1'-cyclization to an unidentified intermediate, which underwent subsequent reduction with  $\text{LiAlH}_4$  to the pentacycle **66** (50%). Similarly,



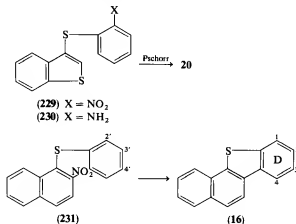
<sup>78</sup> P. Cagniant, M.-M. Briola, and G. Kirsch, *C. R. Hebd. Seances Acad. Sci.* **285C**, 21 (1977).

<sup>79</sup> S. Hauptmann, A. Hantschmann, and M. Scholz, *Z. Chem.* **9**, 22 (1969) [*CA* **70**, 77689 (1969)].

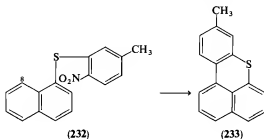
<sup>80</sup> V. N. Gogte, V. S. Palkar, and B. D. Tilak, *Tetrahedron Lett.* **No. 6**, 30 (1960).

sulfoxide **228** gave 2,2'-cyclization (with loss of the elements of  $\text{H}_2\text{O}$ ) on refluxing with  $\text{NaNH}_2$  in toluene to produce the pentacycle **53** (26%).<sup>61</sup> Both references discuss efforts to cyclize diaryl sulfides, sulfoxides, and sulfones.

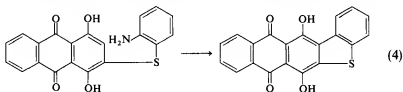
Tilak and co-workers achieved little success in effecting intramolecular thiannulation by means of the Pschorr reaction. Although **229** (55% from thiol **177** and *o*-chloronitrobenzene) was reduced quantitatively to **230** by Raney nickel and hydrogen, the Pschorr reaction occurred in only 2% yield.<sup>57</sup> Similar results were obtained in the conversion of thiol **178** to **27** (1% over-



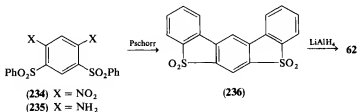
all).<sup>58</sup> Campbell and Keen, however, obtained fair yields of **16** (20%), as well as its D-ring monomethyl derivatives, by Pschorr syntheses from **231** and its 2'-, 3'-, and 4'-methyl derivatives. The intermediate amine was diazotized by ethyl nitrite in glacial HOAc and cyclized in the presence of copper powder or copper bronze.<sup>55</sup> Yields of the methyl derivatives of **16** were 19% for the 2-isomer (m.p. 166.5°C) and 30% for the 4-isomer (m.p. 148°C). From the 3'-methyl derivative of **231** was obtained a chromatographically separable mixture of the 1-methyl (12%) and the 3-methyl (6%) (cf. Tilak thiannulation) derivatives of **16**. Use of the substrate **232**, however, led to Pschorr



cyclization at C-8 (rather than at C-2) to yield the methylbenzothioxanthene (**233**) (Structure proof by desulfurization to 1-*p*-tolynaphthalene).<sup>55</sup> The Pschorr reaction shown in Eq. (4) made a dye intermediate.<sup>81</sup> Grandolino



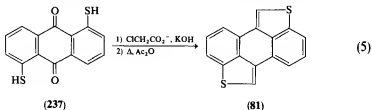
reported the synthesis of **62** by use of a double Pschorr cyclization of the diaminodisulfone **235** (Scheme 13).<sup>82</sup> Yields of 78% for the conversion **234** → **235**, 53–61% for cyclization to **236** (m.p. > 345°C), and 48% for the final step were obtained.



SCHEME 13

Some intramolecular photothiannulations are included in Section III,C,2.

An intramolecular thiannulation procedure<sup>1</sup> was recently used to convert **237** to the perylene thienolog **81** (43%), as shown in Eq. (5).<sup>83</sup> A German patent claimed that oxidation of **237a** yields dyes of structures **237b**.<sup>83a</sup> Other acid-catalyzed intramolecular thiannulations are included in Section III,C,3.

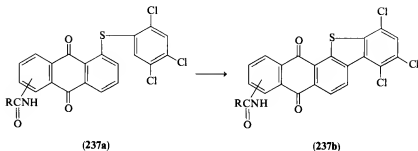


<sup>81</sup> A. T. Peters and B. A. Tenny, *J. Soc. Dyers Colour.* **93**, 373 (1977) [*CA* **89**, 199067 (1978)].

<sup>82</sup> G. Grandolino, *Ann. Chim. (Rome)* **51**, 195 (1961) [*CA* **55**, 21091 (1961)].

<sup>83</sup> F. Wudl, R. C. Haddon, E. T. Zellers, and F. B. Bramwell, *J. Org. Chem.* **44**, 2491 (1979).

<sup>83a</sup> O. Fuchs and D. Wagner, German Patent 1,227,176 (1966) [*CA* **66**, 11857 (1967)].



### C. HOMOANNULATION

In contrast to sulfur bridging and thiannulation, wherein a thiophene (or other heterosulfur ring) is formed, homoannulation involves the addition of one or more carbocyclic rings to the substrate molecule. Intramolecular processes are considered first and intermolecular processes thereafter.

#### 1. Method a: Elbs Reaction

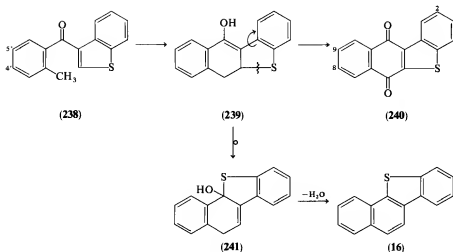
Use of the Elbs reaction to synthesize tetra- and pentacyclic condensed thiophenes was initiated by Buu-Hoï and Nguyen-Hoan<sup>84</sup> and by Werner.<sup>1,85</sup> Probably because of the ease of obtaining starting ketones (*vide infra*), the reaction has been used frequently despite its poor to moderate yields, numerous side products, and the likelihood of skeletal rearrangements. Commonly, the reaction is conducted by thermolysis of a neat aroylbenzo-[*b*]thiophene bearing a methyl or alkylene substituent ortho to the carbonyl group at 340°–450°C (reflux) for 2–3 hr or 380°–420°C for 5–50 min. Products are usually separated by chromatography on alumina. The early observation of Badger and Christie<sup>86</sup> that ketone **238** forms the rearranged product **16** rather than the expected compound **5** alerted research workers to the need for caution in structural assignments. The conversion **238** → **16** has been corroborated by Buu-Hoï *et al.*,<sup>87</sup> who reported a yield of 20%, and by Croisy and Jacquignon (*vide infra*). Scheme 14 shows the proposed pathway for the transformation.<sup>86</sup> Evidence for the intermediacy of **239** is

<sup>84</sup> N. P. Buu-Hoï and Nguyen-Hoan, *Recl. Trav. Chim. Pays-Bas* **67**, 309 (1948).

<sup>85</sup> E. G. G. Werner, *Recl. Trav. Chim. Pays-Bas* **68**, 520 (1949).

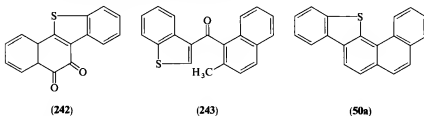
<sup>86</sup> G. M. Badger and B. J. Christie, *J. Chem. Soc.*, 3435 (1956).

<sup>87</sup> N. P. Buu-Hoï, A. Croisy, and P. Jacquignon, *J. Chem. Soc. (C)*, 339 (1969).



SCHEME 14

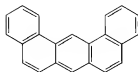
the isolation of quinone **240** (m.p. 215°C), believed to be formed by air oxidation of **239** on the chromatographic column. A control shows that compound **5** does not isomerize to **16** at the reaction temperature. For identification in small amounts, **16** can be oxidized by chromic acid to the 1,2-quinone **242** (m.p. 217°C; quinoxaline derivative, m.p. 230°C). Quinone **240** will not form a quinoxaline derivative.



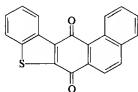
In contrast, Badger and Christie<sup>88</sup> found that ketone **243** undergoes pyrolysis without rearrangement to yield **60** (54%). Had rearrangement occurred by the proposed pathway, one should have obtained **50a** instead.

The structure of product **60** was assigned on the basis of its UV spectrum, which resembled that of its benzolog (**244**), and chromic acid oxidation to a 1,4-quinone (**245**, m.p. 261°C), which was recovered unchanged on heating with *o*-phenylenediamine. Analogously, ketone **246** produced **61** (43%) with-

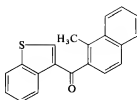
<sup>88</sup> G. M. Badger and B. J. Christie, *J. Chem. Soc.*, 913 (1958).



(244)

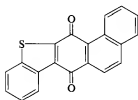


(245)

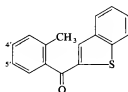


(246)

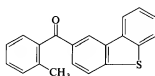
out skeletal rearrangement. The product gave a 1,4-quinone (**247**, m.p.  $256^{\circ}\text{C}$ ) and had a UV spectrum similar to that of its benzolog. Recall that Werner obtained unrearranged **5** from **248**, albeit in only 5–8% yield<sup>85</sup>; his successful use of the Elbs reaction was fortunate. Several patents claim that **249** cyclizes to **47**, which apparently exists in two different crystalline forms (m.p.  $250^{\circ}$  and  $\sim 285^{\circ}\text{C}$ ).<sup>1,89,90</sup>



(247)



(248)



(249)

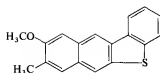
Buu-Hoi and co-workers<sup>91</sup> reported that the presence of a methoxy substituent on the phenyl ring of **238** or **248** does not alter the observations of Werner and of Badger and Christie about cyclization pathways. Thus, the 4'-methoxy-5'-methyl derivative of **248** cyclized without rearrangement to yield **250** (3%) and the 1,4-quinone **251** (10%). Consistent with the suggestion of Badger and Christie that chromatography on alumina fosters oxidation of intermediates of type **239** to 1,4-quinones is the report that no **251** was observed when the reaction mixture was chromatographed on silica gel instead of alumina. Rearrangement did occur for the 4'-methoxy and the 4'-methoxy-5'-methyl derivatives of **238**. The former produced **253** ( $\text{R} = \text{H}$ ) (6%) and the quinone **252** (1%), whereas the latter gave **253** ( $\text{R} = \text{CH}_3$ ; 19%), oxidizable by chromic acid to the 1,2-quinone **254**.

<sup>89</sup> "Beilsteins Handbuch der Organischen Chemie" 3rd and 4th supplement, Vol. 17, p. 761. Springer Verlag, Heidelberg (1974).

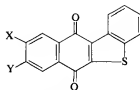
<sup>90</sup> W. H. Cherry, W. Davies, B. C. Ennis, and Q. N. Porter, *Aust. J. Chem.* **20**, 313 (1967).

<sup>91</sup> C. Marie, N. P. Buu-Hoi, and P. Jacquignon, *J. Chem. Soc. (C)*, 431 (1971).



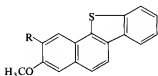


(250)

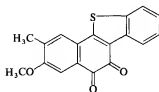


(251) X = MeO; Y = Me

(252) X = H; Y = MeO

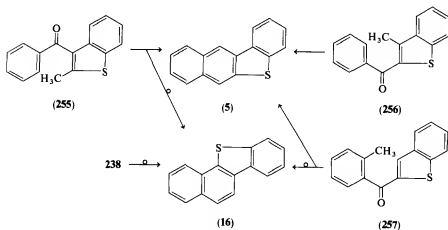


(253)



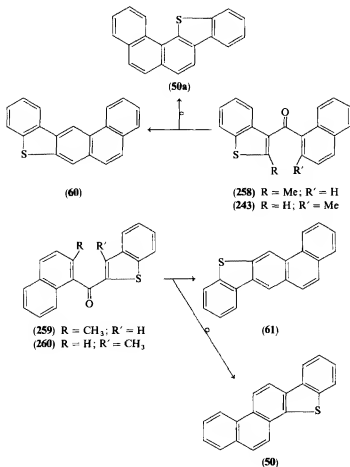
(254)

Croisy and Jacquignon reinvestigated the products formed from the Elbs reactions of 2- and 3-benzoylbenzo[*b*]thiophenes and 2- and 3-(1-naphthoyl)benzo[*b*]thiophenes having methyl substituents at various ortho positions. Only abstracts have been published, but the products apparently depend on both the location of the methyl group and the temperature. Problems also arise from overlooking the fact that the starting ketone may be a mixture of isomers (cf. Faller, *vide infra*). Findings are summarized in Schemes 15 and



SCHEME 15

16.<sup>92,93</sup> Scheme 15 shows that compound **256** cyclizes without rearrangement; **238**, consistent with previous results, cyclizes only with rearrangement, but **255** and **257** lead to mixtures of **5** and **16**. Scheme 16 indicates that **243** gives both **60**, as found by Badger and Christie, and **50a** (major product). Likewise, **258** and **259** give mixtures of products from cyclizations with and



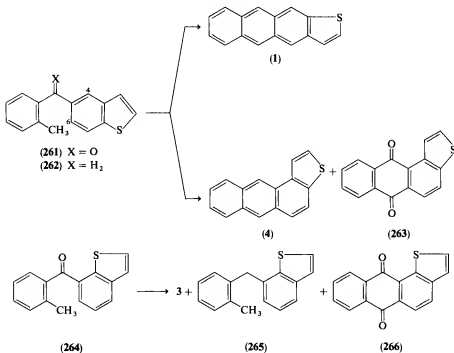
SCHEME 16

<sup>92</sup> A. F. Croisy and P. C. Jacquignon, *Abstracts, Fifth Symposium on Organic Sulphur Chemistry, Lund, Sweden* (1972).

<sup>93</sup> A. F. Croisy and P. C. Jacquignon, in "Organic Sulphur Chemistry" (C. J. M. Stirling, ed.), p. 462. Butterworths, London, 1975.

without rearrangement, whereas **260** yields only **61**. Croisy and Jacquignon also reported the formation of various quantities of an unidentified product.

Faller employed the Elbs reaction on 5- and 7-(*o*-toluyl)benzo[*b*]thiophenes, **261** and **264**, to synthesize thienologs of benz[*a*]anthracene (**95**), wherein the D ring is heterocyclic.<sup>94</sup> Isolated from **261** were **1** (10%) from cyclization at C-6, **4** (25%) from cyclization at C-4, **262** (15%) from attendant reduction, and **263** (12%, m.p. 196°C) from oxidation. Likewise, **264** produced **3** (20%), **265** (23%), and quinone **266** (16%, m.p. 119°C).



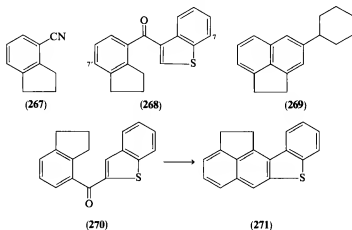
The sources and purities of the ketones used as starting materials in the Elbs reaction must be considered. Compounds **261** and **264**, used by Faller, were prepared from arylmagnesium bromides and aryl nitriles. They should be free of isomeric components. However, 3-arylbenzo[*b*]thiophenes used in studies before 1964 were regularly prepared by Friedel-Crafts arylation of benzo[*b*]thiophene. As noted by Iddon and Scrowston electrophilic substitution into benzo[*b*]thiophene "usually gives a mixture of the 2- and 3-isomers, in which the latter predominates."<sup>95</sup> Earlier workers probably

<sup>94</sup> P. Faller, *C. R. Hebd. Seances Acad. Sci.* **267C**, 543 (1968).

<sup>95</sup> B. Iddon and R. M. Scrowston, in "Advances in Heterocyclic Chemistry" (A. R. Katritzky and A. J. Boulton, eds.), Vol. 11, p. 244. Academic Press, New York, 1970.

assumed that their starting materials, prepared by the Friedel–Crafts method, were isomerically pure. Hence, products and reaction pathways from pre-1964 investigations must be deemed uncertain.

Faller used the Elbs reaction to synthesize C-ring thienologs of cholanthrene and its derivatives and noted that Friedel–Crafts reaction of indan-4-carbonyl chloride with benzo[*b*]thiophene gives two ketones, which in turn cyclize to two products (m.p. 138° and 198°C) in minute yields. However, only the 138°C compound was produced when the ketone intermediate was prepared by reaction of 3-benzo[*b*]thienylmagnesium bromide with nitrile **267**.<sup>96</sup> When all ketones were made by the Grignard method, it was claimed that **268** gave **189** (main product, m.p. 162°C) plus **190** (trace amount, m.p. 142°C), whereas **270** yielded **271** (33%, m.p. 197°C) plus a trace of a phenolic by-product, which formed **271** on heating with Zn and ethanol.<sup>97</sup> The structure of the 162°C product (m.p. given as 165°C from Tilak thiannulation,



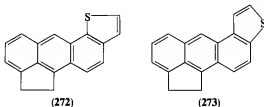
*vide supra*) was assigned from the similarity of its UV spectrum to that of **5** and by desulfurization with Raney nickel to **269**. The 142°C product showed a UV spectrum similar to that of **16**. A confusing aspect of the work is the discrepancy between the melting points 138° and 162°C, which were assigned to the same compound without comment. When a methyl group was present (at C-7 or C-7') in **268**, the corresponding derivatives of **189** and **190** (substituent at C-10 or C-3) were obtained.<sup>98</sup>

<sup>96</sup> P. Faller, *C. R. Hebd. Seances Acad. Sci.* **258**, 2839 (1964).

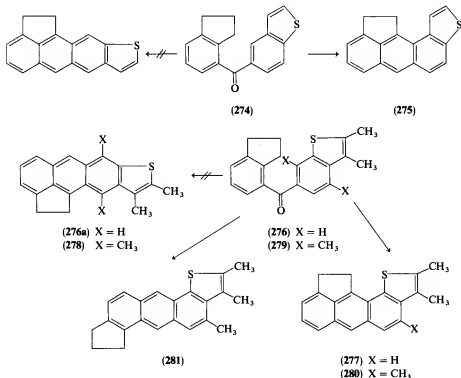
<sup>97</sup> P. Faller, *Bull. Soc. Chim. Fr.*, 3618 (1966).

<sup>98</sup> P. Faller, *C. R. Hebd. Seances Acad. Sci.* **252**, 1034 (1961); **260**, 3686 (1965).

D-Ring thienologs of cholanthrene were also prepared from **267** and bromobenzo[*b*]thiophenes bearing the bromine atom in the benzene ring.<sup>99</sup> The normal Elbs reaction gave **272** (25%, m.p. 173°C) and **273** (8%, m.p.



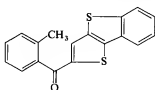
190°C). Regioselectivity was observed in the cyclizations of the ketones **274** and **276**, from which only products with angular aromatic ring structures, **275** (15%, m.p. 212°C) and **277** (16%), were isolated. The strong preference for formation of an angular aromatic system was clearly noted in the Elbs reaction of ketone **279**, which produced **280** (m.p. 150°C) by cyclization with



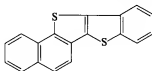
<sup>99</sup> P. Faller, *C. R. Hebd. Seances Acad. Sci.* **262C**, 581 (1966); *Bull. Soc. Chim. Fr.*, 3667 (1966).

attendant demethylation, along with a trace of **281**, formed by cyclization into a methyl group instead of the indan methylene group, and a trace of a 1,4-quinone (m.p. 245°C) of undetermined structure. None of the linearly condensed aromatic compound (**278**) was found. All of the D-ring thienolog products were accompanied by hydrogenated substances and, in largest part, by resins. Structural assignments were based on UV, IR, and PMR spectra. However, there is a marked difference in the UV spectra of the derivatives of **3** and **4** and that of the benzolog (**95**). In fact, the UV spectrum of **272** resembles that of anthracene more closely than that of **95**.

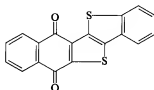
Jacquignon *et al.*<sup>100</sup> cyclized **282** and three of its methyl derivatives to **55** (and methyl derivatives) in yields of 1–3%. The normal structure (**55**), rather



(282)



(283)



(284)

than the rearranged one (**283**), was assigned to the product on the basis of its PMR spectrum and its chromic acid oxidation to the 1,4-quinone **284**.

## 2. Method b: Photocyclization

Carruthers and Stewart were the first to extend the process of stilbene photocyclization to the syntheses of condensed thiophenes. As noted previously, the four monomethyl derivatives (1- to 4-) of **16**, where the methyl group is located in the D ring, were prepared by Tilak and Pschorr thiannulations (*vide supra*). Carruthers and Stewart<sup>101</sup> used photocyclization to prepare samples of five other monomethyl derivatives (5- to 9-) (substituents

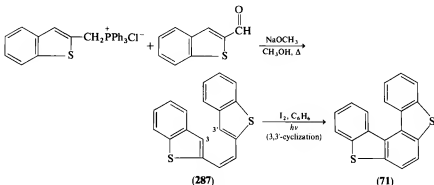
<sup>100</sup> P. Jacquignon, A. Croisy, A. Ricci, and D. Balucani, *J. Chem. Soc., Perkin I*, 734 (1973).

<sup>101</sup> W. Carruthers and H. N. M. Stewart, *J. Chem. Soc.*, 6221 (1965); *Tetrahedron Lett.*, 301 (1965).



III,C,4). The diarylethenes were obtained initially (14% overall) as shown in Scheme 17 (Np =  $\alpha$ - or  $\beta$ -naphthyl).

Wynberg and co-workers synthesized a large number of polycyclic, ortho-condensed thiophenes (thiahelices) by photocyclization using iodine and benzene solvent. Of interest here are the preparations of the tetracycle **11** and the pentacycles **71** and **289**. Scheme 18 shows the pathway to **71** via a Wittig condensation.<sup>104</sup> Product **287** was obtained in cis (34%) and trans (50%) forms. Although only the trans form was used in the cyclization experiment, either isomer undergoes the reaction. The overall yield was 48%, compared to 16% from Tilak thiannulation of *p*-benzenedithiol.<sup>12</sup>



SCHEME 18

Scheme 19 shows an alternative Wadsworth–Emmons condensation (plus cyclization), which produced **289** (54% overall, m.p. 124°C).<sup>105</sup> Compound **26a** was prepared similarly (48% overall).<sup>104</sup> Castle and co-workers<sup>66</sup> followed Scheme 19, but used NaH in glyme in the condensation step (72–90%) between **288** or its 3-isomer and  $\alpha$ - and  $\beta$ -naphthaldehydes. The diarylethenes **290**, from **288**, photocyclized in high yield to **13** (88%) and **22** (75%), whereas those from the 3-thenylphosphonate cyclized in low yield to **15** (32%) and **21** (17%), with extensive tar formation. The possibility that the latter two alkenes cyclized to phenanthro[*c*]thiophenes was ruled out on the basis of the PMR patterns of the products. Low yields on photocyclizations of 3-(styryl)thiophenes had been noted also by Kellogg *et al.*<sup>106</sup> and attributed to the expulsion of thienyl radical during the oxidative process of the dihydro intermediates. Castle and co-workers<sup>56a, 65a, 106a</sup> synthesized

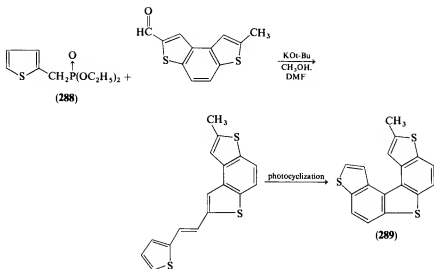
<sup>104</sup> M. B. Groen, H. Schadenberg, and H. Wynberg, *J. Org. Chem.* **36**, 2797 (1971).

<sup>105</sup> P. G. Lehman and H. Wynberg, *Aust. J. Chem.* **27**, 315 (1974).

<sup>106</sup> R. M. Kellogg, M. B. Groen, and H. Wynberg, *J. Org. Chem.* **32**, 3093 (1967).

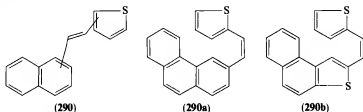
<sup>106a</sup> R. D. Thompson, M. Iwao, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.* **18**, 981 (1981).





SCHEME 19

the 5-methyl derivative of **16**, the 10-methyl derivative of **13** (m.p. 122°C), and the parent tetracycles **16** and **23** (72 and 51%, respectively, for the photocyclization steps) by combinations of the foregoing methods. Compounds **27a** (67%), **64** (72% from **290a**), and **69a** (60% from **290b**) were also prepared.<sup>106b</sup>

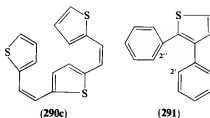


X-ray crystallographic studies of the 1:1 molecular compound of **73** and TCNQ have been reported.<sup>106c</sup> However, the synthesis of **73** apparently has not yet been published; the synthetic procedure of Scheme 19 may have been used. Efforts to obtain **73** by double photocyclization of **290c** failed,<sup>104</sup> which is consistent with calculations of free valence numbers for the excited state of the atoms involved in the cyclization.<sup>106b,106d</sup>

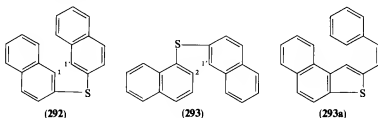
<sup>106b</sup> J. H. Dopper, "The Synthesis and Properties of Some Heterocirculenes," Ph.D. thesis, University of Groningen, V. R. B. Offsetdrukkerij, Groningen, 1974.

<sup>106c</sup> M. Konno, Y. Saito, K. Yamada, and H. Kawazura, *Acta Crystallogr.* **B36**, 1680 (1980).

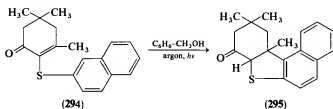
<sup>106d</sup> W. H. Laarhoven, T. J. H. M. Cuppen, and R. J. F. Nivard, *Recl. Trav. Chim. Pays-Bas* **87**, 687 (1968); *Tetrahedron* **26**, 1069 (1970).



Wynberg *et al.*<sup>107</sup> photocyclized 2,3-diphenylthiophene (**291**) (2',2''-coupling, 70% yield) in ether in the presence of air (no iodine). The product was identified by direct comparison with a sample of **28** made by acid-catalyzed cyclization (see Section III.C.3). Product **28** was also obtained from photolysis of 3,4-diphenylthiophene (29%) and in trace amounts from its 2,4-isomer, apparently from initial photoinduced rearrangements to **291**. Surprisingly, **28** also results (17%) from photolysis of 2,3-diiodothiophene in benzene.<sup>107</sup> Dinaphthyl sulfides **292** and **293** underwent photolysis in cyclohexane (with iodine added, N<sub>2</sub> atmosphere) to give **66** (20%), from 1,1'-coupling of the former, and **48** (45%), from 1',2-coupling of the latter.<sup>108</sup> Dopfer also prepared **66** (71%) from photolysis of **293a**.<sup>106b</sup>



Schultz<sup>109</sup> described the transformation of **294** to **295** (89%). Both intramolecular cyclization and hydrogen migration occur. Desulfurization of **295** with Raney nickel or nickel boride gave extensive hydrogenation of the



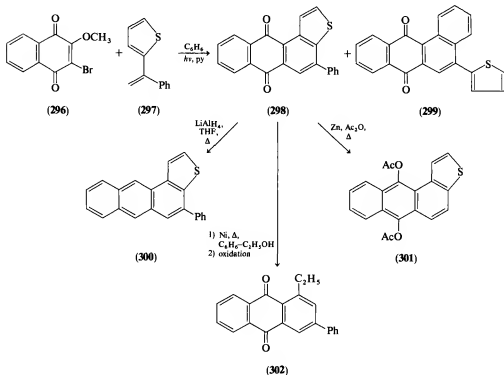
<sup>107</sup> H. Wynberg, H. van Driel, R. M. Kellogg, and J. Buter, *J. Am. Chem. Soc.* **89**, 3487 (1967).

<sup>108</sup> G.-P. Blümer, K.-D. Gundermann, and M. Zander, *Chem. Ber.* **110**, 269 (1977).

<sup>109</sup> A. G. Schultz, *J. Org. Chem.* **39**, 3185 (1974).

naphthalene ring, but these extra hydrogens could be removed by DDQ in refluxing benzene to produce the expected 3-(1-naphthyl)-3,5,5-trimethylcyclohexanone (50%).

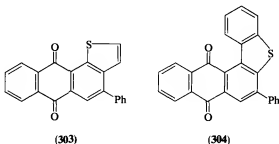
Maruyama *et al.*<sup>110</sup> effected intermolecular photocyclization to substituted, condensed thiophenes. A representative series of reactions is given in Scheme 20. This photochemical Diels–Alder reaction between dienophile **296** and diene **297**, with elimination of the elements of HBr and CH<sub>3</sub>OH from the adducts, gives **298** (62%, m.p. 221.5°C) and **299** (8%). Reactions of **298** produced **300** (32%, m.p. 157°C) and **301** (60%), derivatives of the parent condensed thiophene (**4**). As a partial proof of structure, **298** was desulfurized to **302** (13%). Thermal Diels–Alder reaction between **297** and 1,4-naphthoquinone gave only 6% of **298** (in HOAc), probably because the diene is unstable to heat. The much larger yield of **298** than of **299** was



SCHEME 20

<sup>110</sup> K. Maruyama, K. Mitsui, and T. Otsuki, *Chem. Letts.*, 853 (1977); K. Maruyama, T. Otsuki, K. Mitsui, and M. Tojo, *J. Heterocycl. Chem.*, 17, 695 (1980).

ascribed to preferential  $\pi$ - $\pi$  interaction between **296** and the thiophene ring of **297** in the initial stages of the reaction, a suggestion consistent with results on other furyl and pyrrolyl diene analogs. Photocycloadditions were also conducted with dienes obtained from **297** modified by having (a) a 5-ethyl group on the thiophene ring, (b) *p*-tolyl or *p*-chlorophenyl in place of phenyl, (c) 3-thienyl (instead of 2-thienyl) plus a phenyl, *p*-tolyl, or *p*-chlorophenyl group, (d) a 2-benzo[*b*]thienyl group in place of the 2-thienyl group, and (e) the combination of (d) with a *p*-tolyl group. Products **303** and **304** were obtained in 44 and 32% yields, respectively.



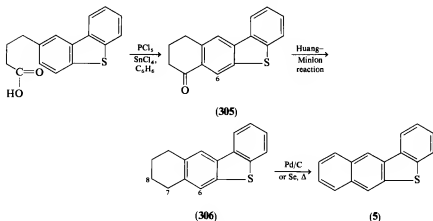
Photocyclizations can be used to obtain a variety of condensed thiophenes that are difficult to prepare by other methods. In some cases yields are very good, but the scale on which syntheses are conducted is usually much less than 1 g due to low solubility of the substrate in the solvent and/or the need to avoid dimerization or polymerization reactions. The reaction **294**  $\rightarrow$  **295** of Schultz, however, is applicable to large-scale synthesis.

### 3. Method *c*: Acid-Catalyzed Cyclization

Method *c* involves the use of either a proton or Lewis acid to effect annulation. Because of the wide variety of procedures employed, this subsection has been subdivided into categories based either on the type of reagent used or on the intermediate compound formed. Most of the examples are correctly listed under homoannulation, but a few acid-catalyzed cyclizations included here strictly belong in Section III,A on sulfur bridging or in Section III,B on thiannulation. Chemically, however, they fit more closely the homoannulation methodology presented in this subsection and are therefore discussed here.

a. *Haworth Procedure*. The Haworth homoannulation procedure used to synthesize polycyclic aromatic hydrocarbons and their derivatives was adapted to the preparation of tetracyclic condensed thiophenes by

various workers before 1952.<sup>1</sup> More recently Campaigne and Osborn,<sup>5,3</sup> as well as Gverdtiteli and Litvinov,<sup>111</sup> repeated the synthesis of **5** by the Haworth method, as presented in Scheme 21 (15% overall), via **305** (m.p. 178°C) and **306** (m.p. 114°C; sulfone, m.p. 190.5°C).<sup>5,3,112</sup> The structure of **5** was established by desulfurization with Ni in ethanol (overreduction) plus Se (dehydrogenation) to 2-phenylnaphthalene (**102**) or alternatively by shaking **5** with Li in ether–benzene at room temperature for 40–50 hr (55%).<sup>111</sup> Under the latter conditions **306**, as well as dibenzothiophene itself, failed to react.<sup>111,113</sup> Treatment of ketone **305** with RMgX led to 7-substituted 9,10-dihydro derivatives of **5** (**307**: R = CH<sub>3</sub>, m.p. 121.5°C; Ph, 100°C; PhCH<sub>2</sub>, 126°C) and 7-substituted derivatives of **5** (**308**: R = CH<sub>3</sub>, m.p. 176°C; *n*-C<sub>3</sub>H<sub>7</sub>, 98°C; *n*-C<sub>4</sub>H<sub>9</sub>, 131°C; Ph, 123°C; PhCH<sub>2</sub>, 179°C) (Scheme 22, R' = R'' = H).<sup>111</sup> Campaigne *et al.*<sup>114</sup> also prepared a series of methyl derivatives of **305**–**307** and **5** with substituents at positions 6, 7, and/or 8. The general procedure followed Schemes 21 and 22 starting with dibenzothiophene or 4-methyldibenzothiophene and succinic anhydride or methylsuccinic anhydride (**309**). Acylation occurred at C-2 of the dibenzothiophene ring in each case, with **309** producing  $\alpha$ -methyl- $\beta$ -aroyl-propionic acid (**310**), which cyclized to **311**. The following products were obtained: **311** (R = H, m.p. 176°C; CH<sub>3</sub>, 119°C), 6-methyl-**305** (m.p. 117.5°C),



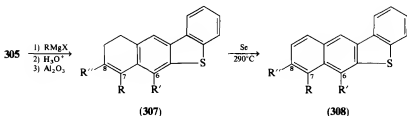
SCHEME 21

<sup>111</sup> D. D. Gverdtiteli and V. P. Litvinov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1340 (1970).

<sup>112</sup> H. Gilman and A. L. Jacoby, *J. Org. Chem.* **3**, 108 (1938).

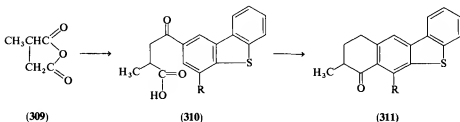
<sup>113</sup> In contrast, Gilman *et al.* [H. Gilman and D. L. Esmay, *J. Am. Chem. Soc.* **75**, 2947 (1953); H. Gilman and J. J. Dietrich, *J. Org. Chem.* **22**, 851 (1957)] reported that dibenzothiophene is converted to biphenyl on refluxing with Li in dioxane and reacts with Li in THF at 25°C.

<sup>114</sup> E. Campaigne, J. Ashby, and S. W. Osborn, *J. Heterocycl. Chem.* **6**, 885 (1969).



SCHEME 22

**307** ( $R, R', R'' = \text{CH}_3, \text{H}, \text{CH}_3$ , respectively, m.p.  $132^\circ\text{C}$ ; all  $\text{CH}_3$ ,  $80^\circ\text{C}$ ;  $\text{CH}_3, \text{CH}_3, \text{H}$ ,  $86^\circ\text{C}$ ;  $\text{CH}_3, \text{H}, \text{H}$ , *vide supra*), **308** ( $R, R', R'' = \text{H}, \text{H}, \text{CH}_3$ , respectively, m.p.  $180^\circ\text{C}$ , sulfone, m.p.  $267^\circ\text{C}$  dec.;  $\text{CH}_3, \text{H}, \text{H}$ , *vide supra*, sulfone,  $286^\circ\text{C}$ ;  $\text{H}, \text{CH}_3, \text{H}$ ,  $96^\circ\text{C}$ ;  $\text{CH}_3, \text{H}, \text{CH}_3$ ,  $194^\circ\text{C}$ , sulfone,  $274^\circ\text{C}$  dec.;  $\text{CH}_3, \text{CH}_3, \text{H}$ ,  $152^\circ\text{C}$ , sulfone,  $262^\circ\text{C}$  dec.;  $\text{H}, \text{CH}_3, \text{CH}_3$ ,  $115^\circ\text{C}$ , sulfone,  $242^\circ\text{C}$  dec.; all  $\text{CH}_3$ ,  $112^\circ\text{C}$ , sulfone,  $208^\circ\text{C}$  dec.), and **306** derivatives (6-methyl, m.p.  $126.5^\circ\text{C}$ ; 8-methyl,  $78.5^\circ\text{C}$ ; 6,8-dimethyl,  $141^\circ\text{C}$ ). Ultraviolet spectral data are given for all of the eight cases of **308**, where  $R, R'$ , and  $R''$  are either  $\text{H}$  or  $\text{CH}_3$ . Various PMR, IR, and mass spectra are also available.<sup>114,115</sup>



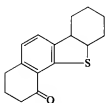
In an effort to direct the Haworth procedure toward the synthesis of ring system **16** or **23** rather than **5**, Cagniant *et al.*<sup>116</sup> followed the general pathway of Scheme 21, but used the starting material **312**. After the condensation and cyclization steps, they obtained a mixture of two ketones, presumed to include **313** or **314**. After further treatment, this mixture gave several substances: (a) a ketone (m.p.  $112^\circ\text{C}$ ) with an aromatic AB system in its PMR and an IR band at  $810\text{ cm}^{-1}$  (expected for two vicinal aromatic H), (b) a minute amount of **5** on heating with Se at  $350^\circ\text{C}$ , (c) a compound  $\text{C}_{16}\text{H}_{16}\text{S}$  (m.p.  $69^\circ\text{C}$ ) after Wolff-Kishner reduction, and (d) an isomer  $\text{C}_{16}\text{H}_{16}\text{S}$  (m.p.  $56^\circ\text{C}$ ) after reduction with  $\text{NaBH}_4$  plus dehydration with polyphosphoric acid (PPA).

<sup>115</sup> See footnote 15 in reference 114.

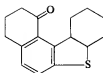
<sup>116</sup> P. Cagniant, M. F. Besse, and D. Cagniant, *Bull. Soc. Chim. Fr.*, 4435 (1971).



(312)



(313)

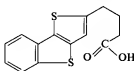


(314)

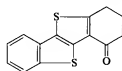
Ricci *et al.*<sup>117</sup> conducted a Haworth annulation on **315** to produce acid **316** and ketone **317** (m.p. 167°C; IR 1680 cm<sup>-1</sup>). In a simplified procedure **317** or even **316** was heated with an intimate mixture of P<sub>2</sub>O<sub>5</sub> at 4–5 mm pressure to give the parent tetracycle (**20**) directly (~80% from **316**; 100% from **317**). With other  $\gamma$ -arylbutyric acids as starting materials, however,



(315)



(316)

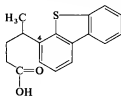


(317)

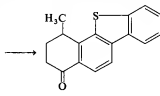
heating with P<sub>2</sub>O<sub>5</sub> gave only the cyclic ketone. However, previous workers also reported the synthesis of **20** (16%) by refluxing a solution of **318** in tetralin with P<sub>2</sub>O<sub>5</sub> or (in 3% yield) by distilling the *S*-acetyl derivative of **318**.<sup>118</sup> As indicated in Section III.C.2, Carruthers and Stewart synthesized the 10-methyl derivative of **16** from acid **319** (prepared from 4-lithiodibenzothiophene and menthyl laevulate by condensation, dehydration, and hydrogenation), which was cyclized to **320** (m.p. 129°C), reduced by the Wolff-Kishner method, and dehydrogenated by elemental sulfur at 240°C.<sup>101</sup>



(318)



(319)

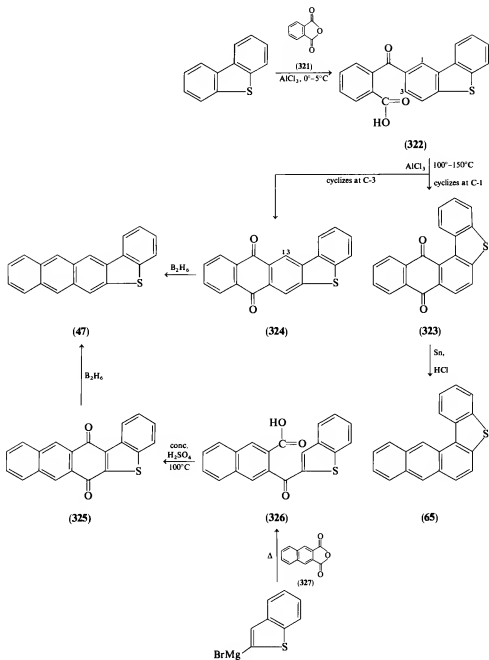


(320)

**b. *o*-Carboxyaroylation Procedures.** The use of phthaloylation (or other *o*-carboxyaroylation) to add two or more rings to a condensed thiophene is illustrated in Scheme 23. Friedel-Crafts reaction of dibenzothiophene

<sup>117</sup> A. Ricci, D. Balucani, and M. Bettelli, *Gazz. Chim. Ital.* **101**, 774 (1971) [*CA* **76**, 113103 (1972)]; A. Ricci, D. Balucani, and B. Berardo, *C. R. Hebd. Seances Acad. Sci.* **275C**, 139 (1972).

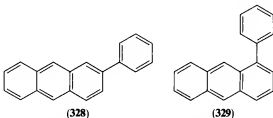
<sup>118</sup> W. Baker, A. S. El-Nawawy, and W. D. Ollis, *J. Chem. Soc.*, 3163 (1952).



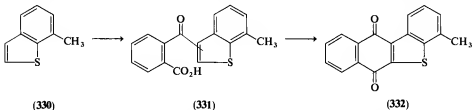
SCHEME 23



phene with **321** to give **322** and its cyclization to **324** (m.p.  $286^{\circ}\text{C}$ ) was reported by Gilman and Jacoby.<sup>112</sup> However, Cherry *et al.*<sup>90</sup> found that both quinones **323** (m.p.  $279^{\circ}\text{C}$ ) and **324** resulted from the Gilman procedure. Also, Gverdtsiteli and Litvinov<sup>119</sup> reported that **322** gave both **47** and **65** after successive treatments with PPA and  $\text{Sn/HCl}$ . The structures of **324** and **325** (obtained from Grignard reaction of anhydride **327** with 2-benzo[*b*]thienylmagnesium bromide to give **326**, followed by cyclization) were established by their reductions to the same aromatic condensed thiophene (**47**).<sup>90</sup> These transformations also clarified the structure of **47**. Structure **323** was corroborated by separate Diels–Alder synthesis from 2-vinylbenzo[*b*]thiophene and 1,4-naphthoquinone (see Section III,C,4).<sup>90</sup> The structures of **47** and **65** were confirmed by Raney nickel desulfurizations to 2-phenylanthracene (**328**) and 1-phenylanthracene (**329**), respectively.<sup>120</sup>



Friedel–Crafts reaction of benzo[*b*]thiophene with **321** was reported before 1950.<sup>1</sup> Litvinov *et al.* extended this reaction to the methyl derivative **330**, which gave keto acid **331** (16%; structure not established<sup>121</sup>), which cyclized to **332** (16%, m.p.  $225^{\circ}\text{C}$ ).<sup>122</sup> Armarego synthesized the pentacycle



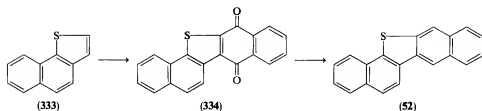
**52** (2% overall) by reaction of **333** with **321**, cyclization of the mixed keto acids to **334** with PPA, and reduction of the quinone to the parent aromatic hydrocarbon by heating with Zn dust, NaCl, and  $\text{ZnCl}_2$  at  $180^{\circ}$ – $320^{\circ}\text{C}$ .<sup>8</sup>

<sup>119</sup> D. D. Gverdtsiteli and V. P. Litvinov, *Soobshch. Akad. Nauk Gruz. SSR* **58**, 333 (1970) [CA 73, 66368 (1970)].

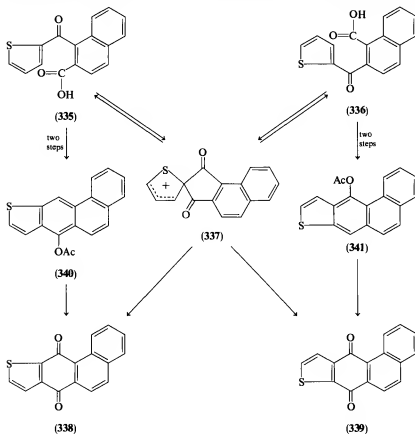
<sup>120</sup> D. D. Gverdtsiteli and V. P. Litvinov, *Soobshch. Akad. Nauk Gruz. SSR* **59**, 333 (1970) [CA 74, 87729 (1971)].

<sup>121</sup> As noted in reference 1 (p. 319) the position of phthaloylation of benzo[*b*]thiophene is uncertain. However, either the 2- or 3-isomer should cyclize to the same quinone.

<sup>122</sup> V. P. Litvinov, D. D. Gverdtsiteli, and E. D. Lubuzh, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 79 (1972).



Newman and Ihrman<sup>123</sup> confirmed the report of Sandin and Fieser<sup>124</sup> that both keto acids **335** and **336** are converted to the same mixture of quinones (**338** and **339**; ratio 1:1.5) by  $P_2O_5$  in  $PhNO_2$  at  $165^\circ C$ . Heating **335** in  $H_2SO_4$  at  $60^\circ C$  for 1 hr gives 90% of **336**, but **336** is recovered unchanged after being heated in PPA at  $60^\circ C$  for 2 hr. These results (Scheme 24)



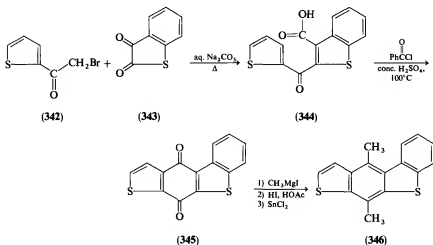
SCHEME 24

<sup>123</sup> M. S. Newman and K. G. Ihrman, *J. Am. Chem. Soc.* **80**, 3652 (1958).

<sup>124</sup> R. B. Sandin and L. F. Fieser, *J. Am. Chem. Soc.* **62**, 3098 (1940).

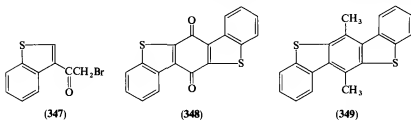
show a common carbonium ion intermediate (337). To prepare pure samples of the quinones, each keto acid was reduced to the corresponding thenyl-naphthoic acid by means of Zn and KOH, cyclized to an acetoxy derivative (340: 71%, m.p. 178.5°C; 341: 76%, m.p. 154°C) by heating with HOAc, Ac<sub>2</sub>O, and ZnCl<sub>2</sub>, and oxidized with CrO<sub>3</sub> in HOAc (338: 30%, m.p. 201°C; 339: 46%, m.p. 165.5°C).<sup>123</sup>

Variations on the aforementioned methods were used by Ghaisas and Tilak<sup>125</sup> to prepare 346, the dimethyl derivative of 11 (Scheme 25). Yields



SCHEME 25

for the successive steps were 57, 74 (345, m.p. 188°C), and 32% (crude, for two steps to 346, m.p. 145°C). Similarly synthesized were 348 (100% crude overall, m.p. 307°C) and 349 (35% crude, m.p. 265°C) from bromo ketone 347 plus 343.<sup>125</sup> Modifications of Schemes 23 and 25 led to the formation of several monosubstituted yellow quinones of structure 240: 2-methyl

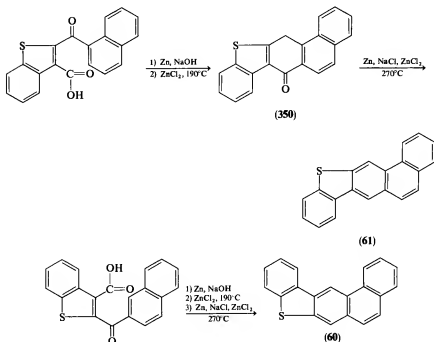


<sup>125</sup> V. V. Ghaisas and B. D. Tilak, *J. Sci. Ind. Res.* **14B**, 11 (1955). See also reference 1.

(m.p. 188°C), 2-ethyl (157°C), 2-bromo (223°C), 8-ethyl (139°C), 9-ethyl (167°C), and 9-bromo (247°C).<sup>125a</sup>

The use of intermediate quinones to give dimethyl derivatives of parent condensed thiophenes is thus a reasonable approach. However, direct reduction of quinones to parent condensed thiophenes (as in the aforementioned cases) has given very low yields.<sup>52a,125a</sup> Better methods for this conversion are needed (see Section III,C,4,b). Tilak and co-workers attempted with little success to circumvent this difficulty by reducing the carbonyl group of the keto acid to a methylene group before effecting ring closure. Two examples are given in Scheme 26. The process actually involves two steps since the ketone (**350**) is not isolated. Overall yields were 13% for **61** and 5% for **60**.<sup>62</sup>

c. *Bradsher Reaction.* As an alternative to the Elbs reaction,<sup>126</sup> the Bradsher reaction was developed by Meth-Cohn and co-workers using

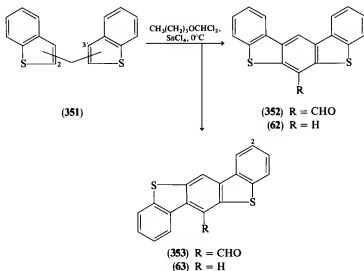


SCHEME 26

<sup>125a</sup> J. N. Chatterjea and R. S. Gandhi, *J. Indian Chem. Soc.* **54**, 719 (1977).

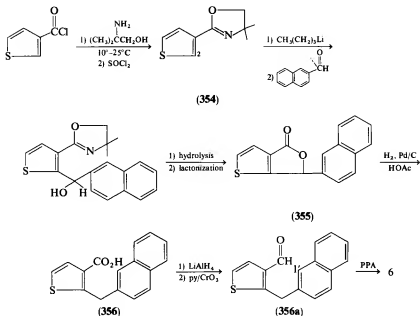
<sup>126</sup> M. Ahmed, J. Ashby, M. Ayad, and O. Meth-Cohn, *J. C. S. Perkin I*, 1099 (1973); M. Ahmed, J. Ashby, and O. Meth-Cohn, *Chem. Commun.*, 1094 (1970).

various diarylmethanes, as shown in Scheme 27. The mixture of isomeric bis(benzo[*b*]thienyl)methanes (**351**) from chloromethylation of benzo[*b*]thiophene in the presence of  $\text{ZnCl}_2$  (57% combined yield) was converted to four products given in order of elution from alumina: **62** (10%), **63** (30%), **352** (20%, m.p. 233°C), and **353** (15%, m.p. 268°C). The aldehydes probably result from formylation of the parent precursors. The use of ethyl dichloro-(ethoxy)acetate (in place of the dichloro ether) on the 2,3'-isomer of **351** likewise gave **353** ( $\text{R} = \text{CO}_2\text{C}_2\text{H}_5$ ) (23%, m.p. 127°C). The 2-methyl derivative of **63** (77%, m.p. 250°C), as well as the tetracycles **5** (15%), its 9-methyl derivative (50%, m.p. 185°C), and **9** (25%), were also prepared.

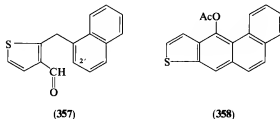


SCHEME 27

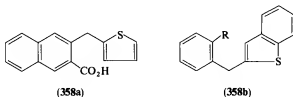
Another modification of the Bradsher reaction was used by Castle and co-workers,<sup>66</sup> as shown in Scheme 28. The oxazoline **354** was used to direct lithiation to C-2 of the thiophene ring. Lactone **355** (58% from **354**) was hydrogenolyzed to **356** (72%). The aldehyde (**356a**, not isolated) gave Bradsher cyclization at C-1' to yield **6** (56% from **356**). Replacing the 2-naphthaldehyde in step 2 by 1-naphthaldehyde led to the intermediate **357**, which underwent Bradsher cyclization at C-2' to produce **8** (57% from the acid precursor of **357**). An alternative route of converting **356** to **6** involves treatment of the former with  $\text{ZnCl}_2/\text{Ac}_2\text{O}$  to give **358** (81%, m.p. 160°C), but action of  $\text{Zn}/\text{NaOH}$  on **358** produced **6** in only 3% yield. By variations on Schemes

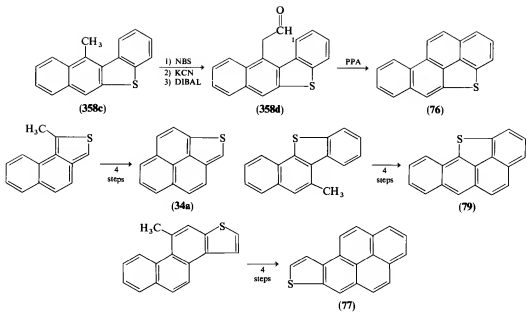


SCHEME 28



26 and 28 Castle recently prepared compounds **358a** and **358b** ( $R = \text{CO}_2\text{H}$ ) and cyclized them to the parent tetracycles **1** and **5** in the manner used with isomeric **356** (respectively, 51 and 58% overall).<sup>56a</sup> The Bradsher reaction on **358b** ( $R = \text{Ac}$ ) produced the 11-methyl derivative of **5** (43%, m.p. 162°C; **358c**).<sup>106a</sup>





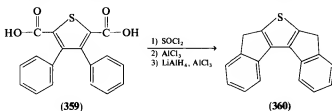
SCHEME 28a

A significant modification of the Bradsher method was introduced recently by Castle to effect homoannulation of structurally appropriate methyl derivatives of condensed thiophenes in four steps (Scheme 28a, where NBS = *N*-bromosuccinimide; DIBAL = diisobutylaluminum hydride).<sup>65a,106a,126a</sup> The main feature is the conversion of a methyl substituent to the  $\text{—CH=CH—}$  unit of a peri-condensed ring structure. Yields reported for the steps in the transformation **358c**  $\rightarrow$  **76** are 76, 72%, and 32% (last two steps). The intermediate aldehyde **358d** undergoes cyclization at C-1. In the same manner, overall yields of 6% for **34a**, 9% for **77**, and 27% for **79** were obtained.

As a synthetic method the Bradsher reaction per se appears to be superior to the Elbs reaction. The direct procedure of Meth-Cohn uses carcinogenic *n*-butyl dichloromethyl ether. The Castle procedure is relatively free of toxic reagents, isomeric precursors, and rearrangements, but numerous steps are involved before the Bradsher reaction is reached. Thus, all of these methods have advantages and shortcomings.

d. *Acid Chloride Cyclizations.* Many of the Haworth and *o*-carboxyaroylation procedures described previously include Friedel-Crafts cyclization of an acid chloride as the final step in the annulation process. This subsection is concerned with cyclizations of acid chlorides (or acids) that do not involve keto acid intermediates.

MacDowell and Patrick<sup>127</sup> effected cyclization of **359** to a diketone (24%, m.p. 335°C) and reduction to **360** (22%, m.p. 216°C) (Scheme 29). However, their sample of **360** appears to be different from the product of m.p. 292°C described by Friedmann, and ascribed structure **360**, from the reaction of sulfur with indene at 180°C.<sup>1,128</sup> MacDowell and Patrick obtained only intractable tar from the Friedmann procedure. A double cyclization was also employed by Cagniant and co-workers (Scheme 30).<sup>129</sup>



SCHEME 29

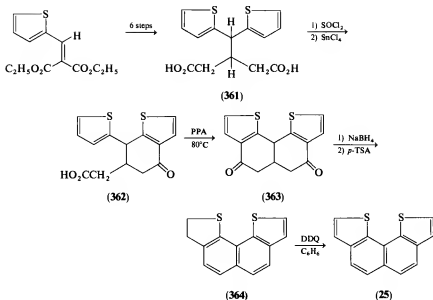
<sup>126a</sup> Y. Tominaga, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.* **18**, 977 (1981).

<sup>127</sup> D. W. H. MacDowell and T. B. Patrick, *J. Heterocycl. Chem.* **4**, 425 (1967).

<sup>128</sup> W. Friedmann, *Ber.* **49**, 50, 683 (1916).

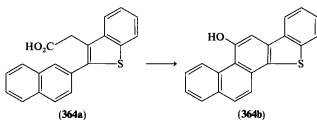
<sup>129</sup> D. Muller, J.-F. Muller, and D. Cagniant, *J. Chem. Res. (S)*, 328 (1977); *J. Chem. Res. (M)*, 3673 (1977).





SCHEME 30

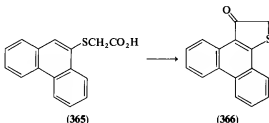
Friedel-Crafts reaction of the difunctional acid chloride of **361** gave exclusively monocyclization to **362** (70%). Compound **363** (obtained as a 1.8:1 mixture of *cis-trans* isomers, 67%) gave a mixture of **364** (54%) and **25** (20%) from reduction plus dehydration. Dehydrogenation of this mixture produced **25** only (50%). Lamberton and Paine<sup>129a</sup> used the acid chloride method to convert acid **364a** to phenol **364b** (42%, m.p.  $\sim 250^\circ\text{C}$ ; methyl ether, m.p.  $163^\circ\text{C}$ ).



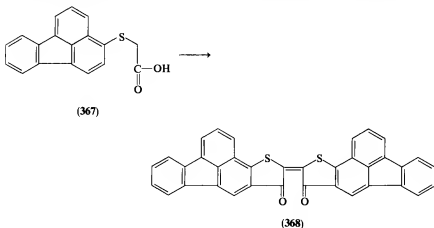
Intramolecular thiannulations have also been conducted by Friedel-Crafts reactions of acid chlorides. As structural proof for **28**, obtained by photocyclization (*vide supra*), Wynberg *et al.*<sup>107</sup> cyclized the acid chloride

<sup>129a</sup> A. H. Lamberton and R. E. Paine, *J. C. S. Perkin I*, 683 (1976).

of **365** to **366** (78%, m.p. 155°C), which was converted to **28** (11%) by reduction with Zn/HOAc. Parent **28** was also oxidized to 9,10-phenanthrenequinone



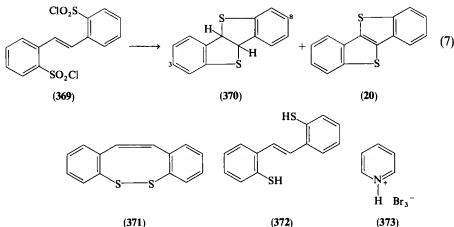
with  $\text{CrO}_3/\text{HOAc}$ . Russian workers likewise cyclized acid **367** and then converted the intermediate ketone to the thioindigoid dye **368** (30%).<sup>130</sup>



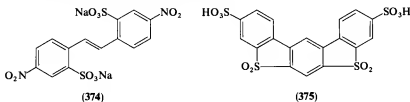
Zherdeva *et al.*<sup>131</sup> discovered a surprising cyclization of disulfonyl chloride **369** with aqueous HI/HOAc at 20°–100°C (Eq. 7). They obtained **370** (42%, m.p. 147°C) and its aromatized parent compound (**20**, 18%, m.p. 217°C), but under other conditions only **20** (79%) was isolated. Probably closely allied to this reaction are the formations of **20** from boiling disulfide **371** with  $\text{Br}_2/\text{CCl}_4$  (67% yield) or from boiling dithiol **372** with *N*-bromosuccinimide and benzoyl peroxide/ $\text{CCl}_4$  (79%).<sup>131</sup> Investigations of **370** consisted of oxidation to a disulfone (m.p. 358°C), desulfurization with Raney nickel/ethanol to bibenzyl, and dehydrogenation by various methods to **20**. Especially effective (96% yield) for dehydrogenation is **373** in boiling HOAc. In

<sup>130</sup> M. I. Shenbor and A. T. Tsaberyabyi, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.* **12**, 1379 (1969) [*CA* **72**, 111140 (1970)].

<sup>131</sup> S. Yu. Zherdeva, A. Ya. Zheltov, T. A. Kozik, and B. I. Stepanov, *Zh. Org. Khim.* **16**, 425 (1980).



an extension of these studies, Zherdeva *et al.*<sup>132</sup> prepared fifteen 3,8-disubstituted derivatives of **20** from the dinitrodisulfonate salt **374** by successive steps (as needed) of (a) reduction of one or both nitro groups to amino groups, (b) diazotization and replacement of an amino group with another substituent, (c) conversion to the disulfonyl chloride, (d) cyclization with HI/HOAc, and (e) dehydrogenation of the crude mixture with **373**. Direct ring closure (sulfur bridging) was observed by VanAllan,<sup>133</sup> who obtained a disulfone disulfonic acid (possibly **375**) (53%) from treatment of *m*-terphenyl (**104**) with 20% oleum or ClSO<sub>3</sub>H at 90°–100°C.

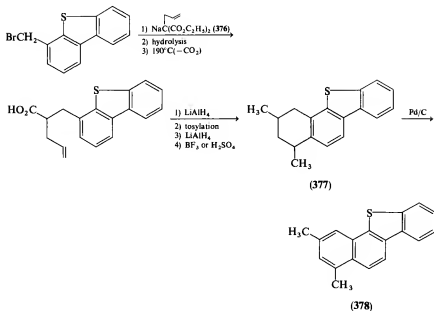


**e. Intramolecular Alkylation.** Gourier and Canonne<sup>134</sup> used a lengthy route for effecting homoannulation by acid-catalyzed intramolecular cyclization as the final step. An example is given in Scheme 31. The actual starting material was dibenzothiophene, which was converted to **377** (80–95%) in

<sup>132</sup> S. Yu. Zherdeva, A. Barudi, A. Ya. Zheltov, and B. I. Stepanov, *Zh. Org. Khim.* **16**, 430 (1980).

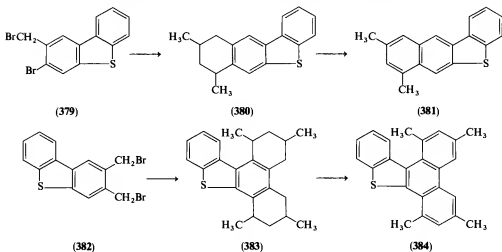
<sup>133</sup> J. A. VanAllan, *J. Org. Chem.* **21**, 1152 (1956); J. E. Jones, J. Spence, and J. A. VanAllan, U.S. Patent 2,937,089 (1960) [*CA* **55**, 19950 (1961)]; Belgian Patent 556,419 (1957) [*CA* **54**, 130 (1960)].

<sup>134</sup> J. Gourier and P. Canonne, *Bull. Soc. Chim. Fr.*, 3110 (1973).

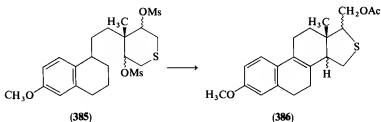


SCHEME 31

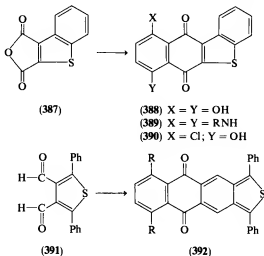
seven steps. Dehydrogenation gave **378** (80–90%, m.p.  $136^\circ\text{C}$ ). Likewise, **379** was transformed to **380**, with displacement of Br from C-3 on cyclization, and then to **381** (m.p.  $156^\circ\text{C}$ ), and **382** gave **383** and **384** (m.p.  $178^\circ\text{C}$ ). The structures of the methyl-substituted aromatic products were consistent with



the observed spectra. Acetolysis of **385** ( $\text{Ms} = \text{CH}_3\text{SO}_2$ ) at  $80^\circ\text{C}$  gives the by-product **386**.<sup>135</sup>



f. *Intermolecular Condensation of Phenols*. Peters and Walker<sup>136</sup> used an  $\text{NaCl}-\text{AlCl}_3$  melt at  $160^\circ-190^\circ\text{C}$  to condense hydroquinone with **387** to obtain hydroxyquinone **388** (56%, dark red needles, m.p.  $258^\circ\text{C}$ ; diacetate, bright yellow needles, m.p.  $242^\circ\text{C}$ ). The vat solution of **388** was heated ( $145^\circ\text{C}$ ) in a sealed tube with an ethanolic solution of a primary amine to produce **389** [ $\text{R} = \text{CH}_3$ , 66%, blue needles, m.p.  $260^\circ\text{C}$ ;  $\text{R} = \text{CH}_3(\text{CH}_2)_3$ , 49%, blue-violet needles, m.p.  $151^\circ\text{C}$ ]. Condensation of **387** with *p*-chlorophenol gave **390** or its isomer (orange-red needles, m.p.  $261^\circ\text{C}$ ; acetate, yellow needles, m.p.  $250^\circ\text{C}$ ). Peyrot *et al.*<sup>137</sup> condensed **391** (obtained in four steps from 2,3-dimethyl-1,4-diphenylbutadiene) with 1,4-dihydroxynaphthalene in *p*-TSA/ $\text{HOAc}$  to give **392** ( $\text{R} = \text{H}$ , m.p.  $300^\circ\text{C}$ ). Similarly obtained were **392** ( $\text{R} = \text{Ph}$ , m.p.  $316^\circ\text{C}$ , 75%;  $\text{R} = \text{OH}$ , m.p.  $364^\circ\text{C}$ , 55%).<sup>138</sup>



<sup>135</sup> T. Terasawa and T. Okada, *Tetrahedron Lett.* **21**, 2549 (1980).

<sup>136</sup> A. T. Peters and D. Walker, *J. Chem. Soc.*, 1429 (1956).

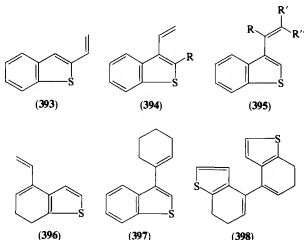
<sup>137</sup> M. Peyrot, D. Villessot, and Y. Lepage, *C. R. Hebd. Seances Acad. Sci.* **282C**, 607 (1976).

<sup>138</sup> D. Villessot and Y. Lepage, *J. Chem. Res. (S)*, 464 (1978); *J. Chem. Res. (M)*, 5538 (1978).

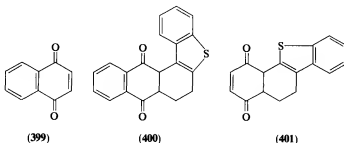
## 4. Method d: Diels–Alder Reaction

The Diels–Alder reaction has been used extensively for the syntheses of condensed thiophenes, especially by Davies and Porter<sup>139</sup> in Australia.

a. *Vinylbenzo[b]thiophenes as Dienes.* Vinylbenzo[b]thiophenes that have been employed as dienes in the Diels–Alder reaction are **393**–**398**. Condensation of **393** with 1,4-naphthoquinone (**399**) gave **400**, which was

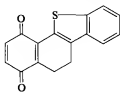


dehydrogenated to the corresponding aromatic quinone by means of chloranil.<sup>90</sup> Heating excess **394** (R = H) with 1,4-benzoquinone in HOAc gave **401** (69%, m.p. 207°C), unchanged on refluxing with HOAc–HCl.<sup>103</sup> From excess 1,4-benzoquinone plus **394** (R = H) was obtained **402** (66%, m.p. 202.5°C; depressed on admixture with **401**). Both **401** and **402** were

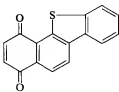


<sup>139</sup> W. Davies and Q. N. Porter, in "Current Trends in Heterocyclic Chemistry" (A. Albert, G. M. Badger, and C. W. Shoppee, eds.), p. 56. Butterworths, London, 1957.

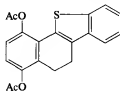
dehydrogenated to **403** (m.p. 198°C) on refluxing with chloranil in xylene.<sup>40,103</sup> Compound **401** gave a negative Zerewitinoff test for active hydrogen and did not dissolve in cold NaOH solution but was converted to **402** on boiling (in air) with aqueous NaOH. Also, warm  $\text{Ac}_2\text{O}-\text{H}_2\text{SO}_4$  gave diacetate **404** (colorless prisms, m.p. 210°C), and reduction of **403** with  $\text{LiAlH}_4$



(402)

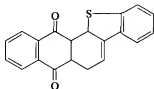


(403)

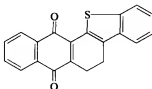


(404)

in THF formed **16** (79%). Condensation of **394** ( $\text{R} = \text{H}$ ) with **399** (molar ratio 1:1.5) produced adduct **405** (63%, pale yellow, m.p. 210°C), whereas a larger excess of **399** (1:3) gave further dehydrogenation to **406** (70%, m.p. 218°C, *vide infra*), which was aromatized by means of chloranil to **407** (69%, m.p. 274°C).<sup>103,139,140</sup> Reductive acetylations ( $\text{Zn}-\text{NaOAc}-\text{Ac}_2\text{O}$ ) of **406** and **407** gave diacetates (m.p. 254° and 311°C).  $\text{SnCl}_2-\text{HCl}-\text{HOAc}$  converted **407** to the anthrone (51%, m.p. 210°C), which was further reduced to the parent pentacycle (**51**, 53%) by means of activated Zn and NaOH. Similarly, **394** ( $\text{R} = \text{H}$ ) condensed with juglone (**408**), lawsone acetate (**409**) (but not

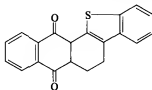


(405)

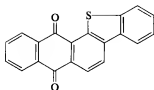


(406)

<sup>140</sup> In references 103 and 139 the structure of **405** was assumed to be the conjugated isomer (**405a**). However, as shown later (ref. 90) the PMR spectrum of the compound showed a multiplet for one proton at  $\delta$  3.94, consistent with the presence of a vinylic proton therein.



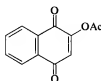
(405a)



(407)



(408)

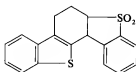


(409)

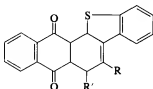


(410)

lawsone itself), benzyne in THF (to give **16**, 14%),<sup>141</sup> and sulfone **410**. The fourth product (**411**) (65%, m.p. 264°C) was reduced with  $\text{LiAlH}_4$  in THF, then dehydrogenated to **54**, and desulfurized to *m*-terphenyl (**104**).<sup>103</sup> Diels-Alder reaction also occurred between **399** and various monomethyl derivatives of 3-vinylbenzo[*b*]thiophene. Thus, **395** in refluxing 1-butanol gave **412** (73%, m.p. 205°C dec., for  $\text{R} = \text{CH}_3$ ;  $\text{R}' = \text{R}'' = \text{H}$ ), (68%, m.p.



(411)



(412)

155°C dec., for  $\text{R} = \text{R}'' = \text{H}$ ;  $\text{R}' = \text{CH}_3$ ), but there was no condensation of **395** for  $\text{R} = \text{H}$ ;  $\text{R}' = \text{R}'' = \text{CH}_3$ .<sup>142</sup> Compound **394** ( $\text{R} = \text{CH}_3$ ) reacts only after extended heating with an excess of **399** to give the 13-methyl derivative of the fully aromatic, rearranged quinone **324** (2%, m.p. 257°C), the structure of which was assigned on the basis of the similarity of its UV spectrum to that of **324**.<sup>142,143</sup> Compound **396** condensed with 1,4-benzoquinone to form adduct **413** (~100%, m.p. 130°C).<sup>144</sup> As a rational synthesis of the parent tetracycle **23**, Davies *et al.* (a) condensed diene **397** with maleic anhydride, (b) dehydrogenated the adduct with  $\text{S}_8$  at 260°C to form **414**, and (c) effected hydrolytic decarboxylation of **414** with  $\text{Ba}(\text{OH})_2/\text{Cu}$  at 200–350°C.<sup>9</sup> Reaction of **397** with 1,4-benzoquinone also produced **415** (75%, m.p. 269°C), even in the presence of excess **397**.<sup>103</sup> Diene **398** condensed with maleic anhydride to form **416** (69%, m.p. 269°C), dehydrogenated with  $\text{S}_8$  to **417** (m.p. 307°C), and hydrodesulfurized to **418**.<sup>145</sup>

<sup>141</sup> T. G. Corbett and Q. N. Porter, *Aust. J. Chem.* **18**, 1781 (1965).

<sup>142</sup> W. H. Cherry and Q. N. Porter, *Aust. J. Chem.* **32**, 145 (1979).

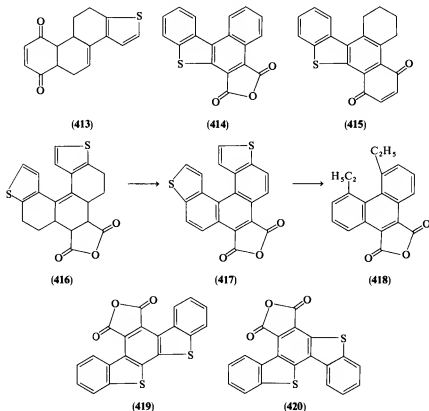
<sup>143</sup> W. H. Cherry, J. T. Craig, Q. N. Porter, and H. G. Upstill, *Tetrahedron Lett.*, 4727 (1972).

<sup>144</sup> I. R. Trehan, R. Inder, and D. V. L. Rewal, *Indian J. Chem.* **14B**, 210 (1976).

<sup>145</sup> D. W. H. MacDowell and R. L. Childers, *J. Org. Chem.* **27**, 2630 (1962).

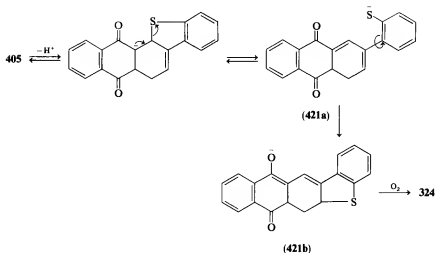


Closely related to the vinylbenzo[*b*]thiophene reactions are the condensations of the bisbenzo[*b*]thienyls **108** and **110** with maleic anhydride in the presence of the dehydrogenating agent chloranil to form **419** and **420**, respectively (55–78%), which are hydrolytically decarboxylated (37–62%) to the parent pentacycles **56** and **54** by means of soda lime at 400°C.<sup>146</sup>



As clarified by Davies and Porter *et al.*, certain nonaromatized Diels–Alder quinone adducts undergo base-catalyzed skeletal rearrangement. Thus, treatment of **405** with warm aqueous ethanolic NaOH in an open flask gave a very dark suspension immediately. This color gradually faded as yellow needles of **324** (94%) were deposited (see reaction of **394**, R = CH<sub>3</sub>, with **399**, above; see also Section III.C,3,b for structure determination of **324**).<sup>90</sup> The proposed mechanistic pathway for the rearrangement **405** → **324** is shown in Scheme 32, wherein ring opening and reclosure may be considered

<sup>146</sup> M. Zander, *Chem. Ztg.* **101**, 507 (1977) [*CA* **88**, 105191 (1978)].

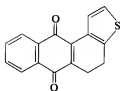


SCHEME 32

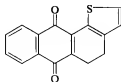
retro-Michael and Michael reactions, respectively.<sup>90</sup> Cherry and Porter<sup>142</sup> did not succeed in trapping anion **421**, but they were able to show that rearrangement is indeed catalyzed by base, but neither by acid nor by oxidizing agents (Scheme 33). Compound **412** was investigated in three different series: (a) for  $R = R' = H$  (i.e., **405**); (b) for  $R = CH_3$ ;  $R' = H$ ; and (c) for  $R = H$ ;  $R' = CH_3$ . In case (a), an unstable quinol (**422**) from double-bond migration was isolated, compound **423** (64%, m.p. 268°C dec.) was identical with purified **406**,<sup>147</sup> and **424** is the same as **407**. For the conversion **412** → **425** the basic solution became crimson in the absence of  $O_2$ , changed to yellow on addition of  $HCl$ , and then reverted to crimson when  $FeCl_3$  was added. The unsubstituted quinone **425** was obtained as crimson needles, which changed to brown on heating (m.p. 265°C dec.). Step 6 [successful only in cases (a) and (c)] was effected with  $NaOH$ -DMF in air, by warming in DMSO, on treatment with chloranil, or on heating at 200°C for 1 min. Evidence for the presence of an angular methyl group in **425** [case (b)] is found in the mass spectrum (base peak at  $(M-16)$  for loss of  $CH_4$ ), the PMR spectrum (3-proton singlet at  $\delta$  1.28), the failure to undergo dehydrogenation by any of the step 6 procedures, and the conversion to **324** on heating with Se. Physical and spectral data are given for the various methyl derivatives, including **426** (61%, yellow needles, m.p. 248°C) and **424** (6-methyl: 63%, orange needles, m.p. 278°C; 7-methyl: 67%, orange needles, m.p. 272°C).

<sup>147</sup> It is claimed that the product of m.p. 218°C (**406**) contains a contaminant which can be removed by TLC to give purified sample, m.p. 268°C (**423**,  $R = R' = H$ ).





(426a)

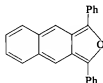


(426b)

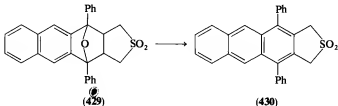
c. *Thiophene Sulfones as Reactants.* Certain thiophene sulfones are important reactants in the Diels–Alder condensation. Two commonly used examples are 2,5-dihydrothiophene sulfone (**427**), which functions as a dienophile only, and benzo[*b*]thiophene 1,1-dioxide (**410**), which can function as either a dienophile or a diene (or both, in self-condensation). Cava and Van Meter<sup>148</sup> condensed **427** with **428** in refluxing benzene to give the adduct **429** (100%), which was converted to tetracycle **430** (82%, m.p. 289°C)



(427)



(428)



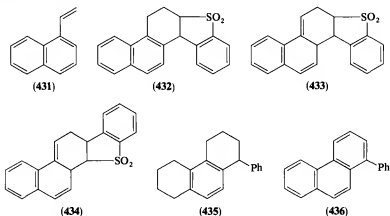
(430)

on heating with HBr–HOAc. Davies and Porter<sup>149</sup> reacted **410** with 1-vinylnaphthalene (**431**) in refluxing toluene (containing a trace of polymerization inhibitor). The adduct (75%, m.p. 277°C) was formulated as **432**. Cross-conjugated structures (**433** and **434**) were rejected because the adduct did not isomerize on being heated with HCl–HOAc. The skeletal structure of **432** was selected on the basis of the following sequential transformations: (a) deoxygenation of the sulfone by means of LiAlH<sub>4</sub> in THF, (b) aromatization to parent compound **49** (73% from **432**) with Se at 300°C, (c) hydrodesulfurization to C<sub>20</sub>H<sub>22</sub> (probably **435**) with W-4 Raney nickel plus ethanol,

<sup>148</sup> M. P. Cava and J. P. VanMeter, *J. Org. Chem.* **34**, 538 (1969).

<sup>149</sup> W. Davies and Q. N. Porter, *J. Chem. Soc.*, 459 (1957).

and (d) finally dehydrogenation with Se to 1-phenylphenanthrene (**436**). Sulfone **410** resisted condensation with either 2-vinylnaphthalene or dicyclohex-1-enyl.



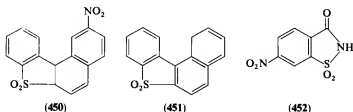
The self-condensation of **410** was observed independently by Bordwell *et al.* and Davies *et al.* in 1951–1952.<sup>1,9,150</sup> It was indicated that the 6-nitro derivative of **410** does not undergo self-condensation. However, Davies and Porter<sup>151</sup> have since found that **410** (acting as a diene) will condense with its 6-nitro derivative (acting as a dienophile) and that dimerization will occur with the 4- and 5-nitrosulfone isomers. Some of the transformations that they reported are presented in Scheme 34 (for the 5-nitro system). The oxidation of **437** to **438** was accompanied by the formation of a trace of **439** (m.p. 360°C). Conversion of **441** (75% from **438**) into **445** serves to establish the skeletal structure of the former.<sup>150</sup> Reaction of **410** with **438** gave the three expected products: **445** (21%), **440** (as shown; 28%, m.p. 212.5°C), and **441** (16%). Clarification of the position of the nitro group as C-10 in **440** was accomplished by degradation to the known saccharin derivative **446**. The sequence **441** → **442** → **439** serves as a convenient method for effecting aromatization, albeit in only moderate yield. An erratic aspect of the condensation reactions of **438** was noted in that small, but variable yields of amines **443** and **444**, and probably the monoamine from **441**, were isolated from accompanying reductive processes. In the 4-nitro system these authors isolated dinitrosulfones **447** (3% from H<sub>2</sub>O<sub>2</sub> oxidation, m.p. 272°C) and **448** (85% from self-condensation). In the 6-nitro series, condensation with **410** produced **445** (16%), **449** (29%, m.p. 269.5°C), and **450** (1%, m.p.

<sup>150</sup> F. G. Bordwell, W. H. McKellin, and D. Babcock, *J. Am. Chem. Soc.* **73**, 5566 (1951); W. Davies, N. W. Gamble, F. C. James, and W. E. Savage, *Chem. Ind.*, 804 (1952).

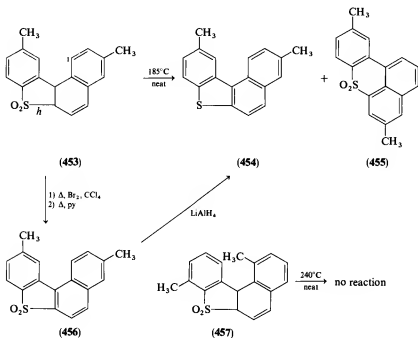
<sup>151</sup> W. Davies and Q. N. Porter, *J. Chem. Soc.*, 826 (1957).



(as before), reduced to the aminosulfone (m.p. 267°C), and reductively deaminated to the known **451**. Compound **449** was oxidized separately to the known nitrosaccharin **452**. The structure of **450** (ostensibly formed by action of the 6-nitrosulfone as a diene) was not investigated.



To gain further insight into the self-condensation reactions of **410** the Australian workers dimerized its 5- and 7-methyl derivatives to the 3,10- (**453**) and 1,8-dimethyl (**457**) derivatives of **445**.<sup>152</sup> The former product was subjected to the transformations shown in Scheme 35. Compound **454** (7%

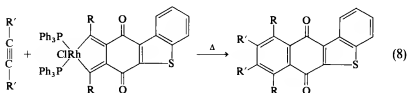
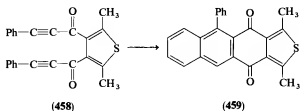


SCHEME 35

<sup>152</sup> W. Davies, B. C. Ennis, and Q. N. Porter, *Aust. J. Chem.* **21**, 1571 (1968).

from pyrolysis, m.p. 128°C) was identified via sulfone **456** (m.p. 271°C). It was suggested that **454** forms from dehydration of **453** to give a sulfoxide, which undergoes disproportionation to **454** and **456**. Compound **455** is visualized as being formed by a separate pathway involving fission of bond *h* in **453** and recyclization at C-1. Consistent with this route to **455** is the fact that **457** is recovered (88%) virtually unchanged upon being heated.

d. *Intramolecular Cyclization.* Müller and Winter<sup>153</sup> used an intramolecular Diels–Alder reaction to convert **458** to **459** (58%) in ethanol at 70°C. They also reacted an Rh complex with disubstituted acetylenes to give quinones, as in Eq. (8) (see sulfur bridging, Section III,A,2).<sup>35</sup>



R = C<sub>2</sub>H<sub>5</sub> or Ph; R' = Ph or CO<sub>2</sub>CH<sub>3</sub>

### 5. Method e: Miscellaneous Cyclizations

Nicolaides prepared **460** (18%, m.p. 198°C) and converted it to its parent pentacycle (**59**, 88%) and its quinone (**461**, 70–75%, m.p. 231°C), as shown in Scheme 36.<sup>154</sup> Gotthardt and Christl<sup>155</sup> used 1,3-dipolar cycloaddition on the route to **142** (69% overall, yellow, m.p. 203°C) (Eq. 9). Fields<sup>156</sup> patented a procedure for reacting thiophene with benzyne (presumed to be

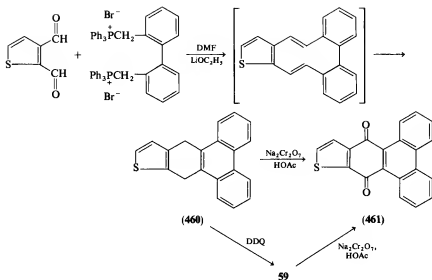
<sup>153</sup> E. Müller and W. Winter, *Justus Liebigs Ann. Chem.*, 605 (1975).

<sup>154</sup> D. N. Nicolaides, *Synthesis*, 675 (1976).

<sup>155</sup> H. Gotthardt and B. Christl, *Tetrahedron Lett.*, 4751 (1968); H. Gotthardt, C. M. Weiss-huhn, and B. Christl, *Chem. Ber.* **111**, 3037 (1978).

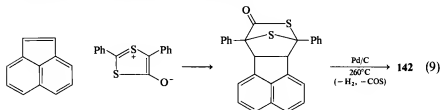
<sup>156</sup> E. K. Fields, U.S. Patent 3,514,458 (1970) [*CA* **73**, 35214 (1970)].





SCHEME 36

formed by thermolysis of phthalic anhydride at 600°–800°C) to give “benzonaphthothiophene” and other products.

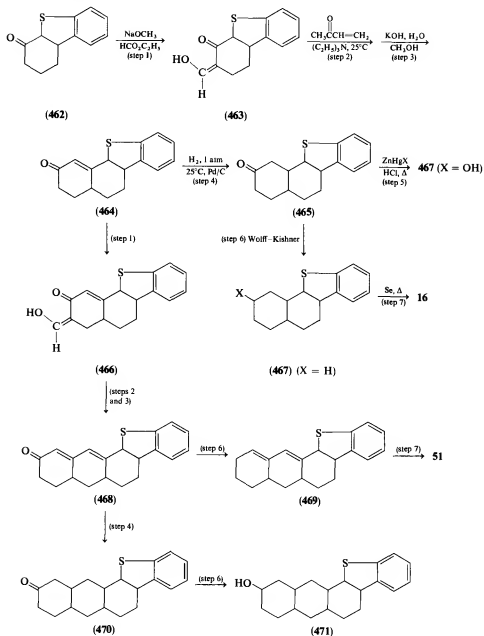


Sastry and Tilak<sup>157</sup> employed base-catalyzed condensations to effect conversion of ketone **462** to the tetracyclic unsaturated ketone **464** and its congeners of system **16** and then to the pentacyclic analogs of system **51** (Scheme 37). Data for compounds formed are as follows: **464** (96% from **463**, m.p. 176°C), **465** (97%, 171°C), **466** (86%, 146°C), **467** (66%, 68°C for X = H; 61%, 149°C for X = OH), **16** (75%), **468** (76%, 217°C), **469** (73%, 158°C), **51** (93%), **470** (84%, 207°C), **471** (60%, 196°C).

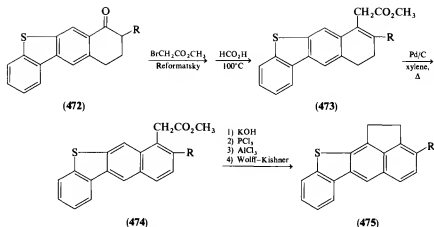
Campaigne *et al.*<sup>158</sup> introduced a five-membered carbocyclic ring by annulation of the ketone precursor **472** (Scheme 38). For the *a* and *b* series, respective results obtained are **473** (71 and 55%), **474** (80%, m.p. 99°C; 80%,

<sup>157</sup> G. R. N. Sastry and B. D. Tilak, *J. Sci. Ind. Res.* **20B**, 286 (1961).

<sup>158</sup> E. Campaigne, J. Ashby, and G. F. Bulbenko, *J. Heterocycl. Chem.* **7**, 1175 (1970).



SCHEME 37

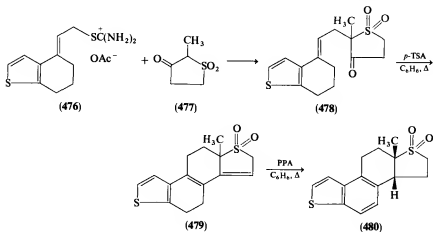


a series: R = H; b series: R = CH<sub>3</sub>

SCHEME 38

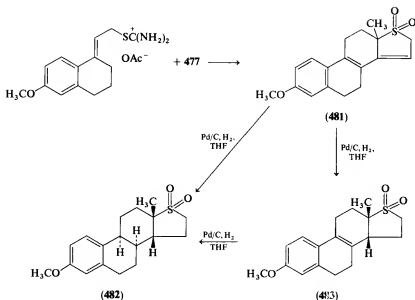
m.p. 182°C), and **475** (62%, m.p. 166°C; 62%, m.p. 188°C). Some hydrolysis products of **473** were also reported.

Jogdeo and Bhide<sup>159</sup> synthesized steroid analogs bearing one or two thiophene rings by the transformations shown in Schemes 39 and 40. Compound **478** (69% yield) cyclized to **479** (85%, resistant to catalytic hydro-



SCHEME 39

<sup>159</sup> P. S. Jogdeo and G. V. Bhide, *Steroids* **34**, 619, 729 (1979); *India, AEC, Bhabha At. Res. Cent. [Rep.] BARC-764*, 96 (1974) [*CA* **82**, 125517 (1975)].



SCHEME 40

genation), which isomerized to **480** (40%, m.p. 183°C). Yields obtained in Scheme 40 are **481** (87%), **482** (80% from **481**, 70% from **483**), and **483** (71%). The conversion **483** → **482** was also accomplished (75%) by means of  $\text{CF}_3\text{CO}_2\text{H}/(\text{C}_2\text{H}_5)_3\text{SiH}$ . Mass spectra are reported for some of the compounds.<sup>160</sup>

#### D. MISCELLANEOUS SYNTHESSES

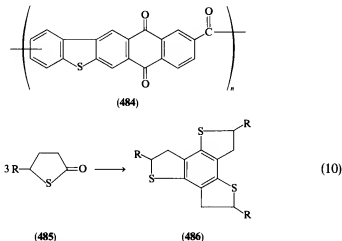
Messerle and Musina<sup>161</sup> reported the formation of a polymer of structure **484** ( $n = 8-15$ ) from heating dibenzothiophene with trimellitic acid trichloride in nitrobenzene or tetrachloroethane. Proetzsch *et al.*<sup>162</sup> effected trimerization of **485** at high pressure (15 kbar,  $1.5 \times 10^4$  atm) and elevated temperature (170°–200°C) to produce **486a** (40–50%, m.p. 184°C) and **486b** (2%, liquid) plus dimers (Eq. 10). Compound **486a** was dehydrogenated to the parent aromatic structure (**33**) by chloranil in toluene. Blümer *et al.*<sup>108</sup> observed skeletal rearrangement and ring closure of dinaphtho[2,1-*b*:1',2'-*d*]-thiophene (**66**) in an  $\text{AlCl}_3/\text{NaCl}$  melt (or, less effectively, with  $\text{AlCl}_3$  in

<sup>160</sup> P. S. Jogdeo, M. S. Chadha, and G. V. Bhide, *Steroids* **35**, 9 (1980).

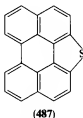
<sup>161</sup> P. E. Messerle and T. K. Musina, U.S.S.R. Patent 504,803 (1976) [*CA* **85**, 6608 (1976)].

<sup>162</sup> R. Proetzsch, D. Bieniek, and F. Korte, *Tetrahedron Lett.*, 543 (1972); *Z. Naturforsch.* **31B**, 529 (1976).

boiling benzene). Dinaphtho[1,2-*b*:2',1'-*d*]thiophene (**53**, 11%) and the hexacyclic compound **487** (9%) were obtained. Also, dinaphtho[1,2-*b*:1',2'-*d*]thiophene (**48**) gave **53** (13%), but no **487**. It was proposed that **48** is an intermediate in the conversion of **66** to **53**.

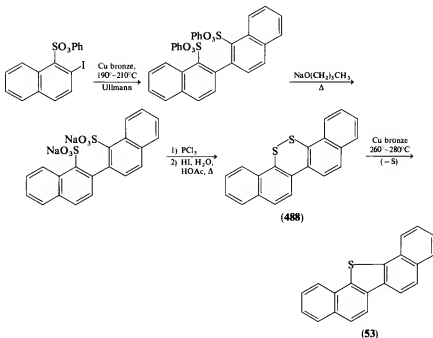


a series: R = H; b series: R = CH<sub>3</sub>



By combining condensation and selective desulfurization steps, Armarego synthesized **53** by the route shown in Scheme 41.<sup>8</sup> Reported percentage yields for the five steps are 95, 31, 65, 96, and 50, respectively. Although Scheme 41 does not constitute structural proof for the Armarego product, the melting point (256°C) of the final product is consistent with that (253°C) of **53** obtained by Wilputte and Martin<sup>61</sup> from intramolecular thiannulation of **228** (*vide supra*). The latter authors proved the structure of their product by Raney nickel desulfurization to give biaryl **153**. In an early study Henriques postulated that **53** results from treatment of **489** with H<sub>2</sub>SO<sub>4</sub> at 100°C.<sup>1,162a</sup> As noted by Hartough and Meisel, the mechanism of such a transformation is not clear. In fact, the melting point of Henriques's product (147°C) and

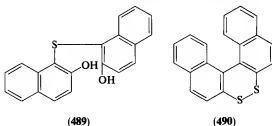
<sup>162a</sup> R. Henriques, *Ber. Dtsch. Chem. Ges.* **27**, 2993 (1894).



SCHEME 41

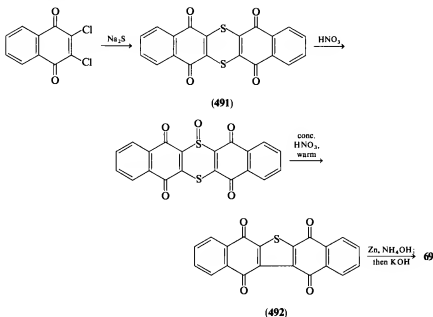
its blue-green coloration on dissolution in concentrated  $\text{H}_2\text{SO}_4$  are inconsistent with the observations of Armarego and imply that Henriques's postulation was incorrect.

Additional study is needed to establish the structural reliability of the copper-promoted conversion represented by **488**  $\rightarrow$  **53**. Another example of this reaction is the transformation **490**  $\rightarrow$  **66** (m.p.  $202^\circ\text{C}$ )<sup>1,163</sup> Alternative syntheses of **66** yielded products of similar melting points ( $202^\circ$ – $210^\circ\text{C}$ ).<sup>52,80</sup> Solely on the basis of melting point ( $250^\circ\text{C}$ ), however, the minor product



<sup>163</sup> H. J. Barber and S. Smiles, *J. Chem. Soc.*, 1141 (1928).

from reaction of sulfur with naphthalene in a hot tube<sup>1,164</sup> is more likely to be **53** or **69** (m.p. 254°C)<sup>61</sup> than **66**, as indicated earlier. In fact, **69** was prepared by a sulfur-bridging condensation plus subsequent selective desulfurization, which, *prima facie*, should be devoid of structural rearrangements (Scheme 42).<sup>61,165</sup> The product (15% from **492**) was desulfurized to **153**. Oxidative desulfurization of **491** to **492** (48%) by H<sub>2</sub>O<sub>2</sub>/HOAc has also been reported.<sup>166</sup>



SCHEME 42

## ACKNOWLEDGMENTS

The largest part of the library investigation for this chapter was conducted during the period from July 1979 to July 1980, while the author was on sabbatical leave in Melbourne, Australia, at La Trobe University (as a visiting professor of organic chemistry) and the University of Melbourne (as senior associate in organic chemistry). The author takes pleasure in acknowledging the considerable assistance provided by these institutions (as well as by the University of Oregon for granting his leave) in the initial work on this review.

<sup>164</sup> M. Lanfry, *Compt. Rend.* **152**, 1254 (1911).

<sup>165</sup> K. Brass and L. Köhler, *Ber.* **55**, 2543 (1922).

<sup>166</sup> K. Fickentscher, R. Wittmann, and H. J. Roth, *Arch. Pharm. (Weinheim)* **302**, 53 (1969) [*CA* **70**, 106439 (1969)].

The 2*H*- and 3*H*-Pyrroles

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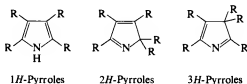
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## I. Introduction

Three classes of pyrroles have been identified (Scheme 1): the familiar aromatic  $1H$ -pyrroles and the less familiar  $2H$ - and  $3H$ -pyrroles. The latter two classes, described in the early literature both as "isopyrroles" and as "pyrrolenines," are nonaromatic due to the tetrahedral carbon atom in the ring, and their chemical properties are thus expected to be very different from those of their  $1H$  counterparts. The  $2H$ - and  $3H$ -pyrrole ring systems



SCHEME 1

are most familiar as intermediates in general pyrrole chemistry.<sup>1</sup> 2H-Pyrroles are believed to be involved in biosynthesis, e.g., of uroporphyrinogen III, the precursor of the natural cyclic tetrapyrrolic pigments.<sup>2</sup> Isopyrroles can be isolated when the tetrahedral carbon atom is fully substituted. Although some aspects of their synthesis and chemistry have appeared in general reviews on pyrroles,<sup>3,4</sup> they have not previously been the subject of a separate, comprehensive treatment.

In this chapter *Chemical Abstracts* have been covered by indexes to mid-1980 and by a computer "on-line" search to September 1981. A few more recent references have been included directly from journals. This review covers 2H- and 3H-pyrroles that have been isolated or characterized spectroscopically, but protonated pyrroles (which have been reviewed elsewhere<sup>5</sup>) and transient isopyrrole intermediates in the electrophilic substitution of 1H-pyrroles are considered to be outside its scope. Pyrroles protonated at the 2-position have been isolated as stable salts.<sup>5a</sup> Also excluded are the numerous pyrrolic compounds with exocyclic double bonds and benz-fused compounds (the 2H- and 3H-indoles).

It is interesting that, although 2H-pyrroles have been known since the beginning of the century and have been described in numerous papers, the 3H compounds have been positively characterized only quite recently<sup>6</sup> and have received little attention since. This is probably due in part to the thermodynamic instability of the 3H-pyrroles relative to their 2H-isomers,<sup>7</sup> but it is also apparent that no serious attempts have been made to develop general synthetic routes to the 3H compounds.

## II. Synthesis of 2H- and 3H-Pyrroles

The most important general method for preparing isopyrroles is by reaction of electrophiles with 1H-pyrroles. Other methods include cyclization of open-chain compounds, 1,3-dipolar cycloadditions using nitrile ylides, and preparations from pyrrolines.

<sup>1</sup> A. R. Katritzky and J. M. Lagowski, "The Principles of Heterocyclic Chemistry," Academic Press, New York, 1968.

<sup>2</sup> M. Akhtar and P. M. Jordan, in "Comprehensive Organic Chemistry" (D. H. R. Barton and W. D. Ollis, eds.), Vol. 5, p. 1131 *et seq.* Pergamon, Oxford, 1979.

<sup>3</sup> G. P. Gardini, *Adv. Heterocycl. Chem.* **15**, 67 (1973).

<sup>4</sup> J. M. Patterson, *Synthesis*, 281 (1976).

<sup>5</sup> R. A. Jones, *Adv. Heterocycl. Chem.* **11**, 383 (1970).

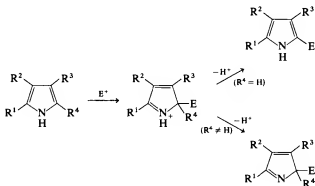
<sup>5a</sup> R. Gassner, E. Krumbholz, and F. W. Steuber, *Liebigs Ann. Chem.*, 789 (1981).

<sup>6</sup> W. E. McEwen, T. T. Yee, T. K. Liao, and A. P. Wolf, *J. Org. Chem.* **32**, 1947 (1967).

<sup>7</sup> J. L. Wong, M. H. Ritchie, and C. M. Gladstone, *J. C. S. Chem. Commun.*, 1093 (1971).

A. FROM 1*H*-PYRROLES AND ELECTROPHILES

During normal electrophilic substitution of pyrroles, the isopyrrole intermediate (Scheme 2) undergoes rearomatization by loss of a proton to give a 1*H*-pyrrole as the product. If, however, the electrophile adds to a carbon already bearing a substituent, rearomatization is not possible, and an isopyrrole may be isolated. Usually, this is a 2*H* form, although occasionally the 3*H* form is a coproduct.<sup>8</sup>



SCHEME 2

Electrophiles that have been used include alkyl halides (usually with the pyrrolylmagnesium halide rather than a free pyrrole), dichlorocarbene, halogenating agents, and oxidizing agents. The approach has been restricted almost entirely to alkyl-, aryl-, and halopyrroles and suffers from the fact that several different products may be formed together, requiring lengthy separation procedures. Yields vary from a few percent in some reactions to more than 90% in others, so preparatively the method can be very attractive.

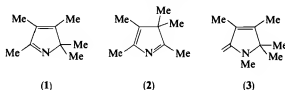
## 1. Methyl Iodide with Base

Heating the sodium salt of pyrrole-2-carboxylic acid with methyl iodide in a sealed tube at 120°C gave the first example of an isopyrrole, formulated<sup>9</sup> as **1** or its isomer (**2**). The same compound, having a menthol- or camphor-like odor, was isolated together with a methylenepyrroline formulated as **3** on treatment of 2,3,4,5-tetramethylpyrrole with methyl iodide and potassium

<sup>8</sup> J. L. Wong and M. H. Ritchie, *J. C. S. Chem. Commun.*, 142 (1970).

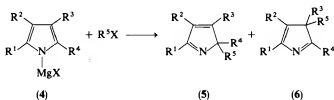
<sup>9</sup> G. Ciamician and F. Anderlini, *Gazz. Chim. Ital.* **18**, 588 (1888); *Ber. Dtsch. Chem. Ges.* **21**, 2855 (1888).

carbonate in a sealed tube.<sup>10</sup> The pyrroline (3) was probably derived from the 2*H*-pyrrole (1) by further reaction with methyl iodide, as had been reported earlier by Anderlini.<sup>11</sup> Similar treatment of less substituted pyrroles had given only complex mixtures, although the pyrroline (3) was identified among the products from 2,3,5-trimethylpyrrole.<sup>12</sup>



## 2. Pyrrolylmagnesium Halides with Alkyl Halides

This reaction has been the subject of a number of conflicting reports, but it has now been shown that a mixture of 2*H*- (5) and 3*H*-pyrroles (6) is formed (Scheme 3); the structures of these compounds have been assigned unambiguously by separation of the isomers by GLC and characterization by UV, IR, and <sup>1</sup>H NMR spectroscopy.<sup>8</sup>



SCHEME 3

Generally, the preformed pyrrolylmagnesium halide (4) is refluxed in ether with an alkyl halide, the acid-soluble isopyrrole mixture being readily separated from 1*H*-pyrroles by extraction. As described in the earliest reports of this reaction,<sup>10,13-15</sup> products were isolated by fractional distillation and characterized as picrates, although the authors were generally

<sup>10</sup> G. Plancher and T. Zambonini, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* [5] **22**, 11, 708 (1913) [CA **8**, 1764 (1914)].

<sup>11</sup> F. Anderlini, *Ber. Dtsch. Chem. Ges.* **22**, 2506 (1889); *Gazz. Chim. Ital.* **20**, 57 (1890).

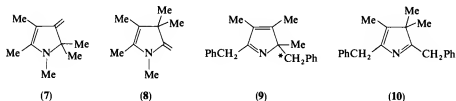
<sup>12</sup> G. Plancher and C. Ravenna, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* [5] **22**, 11, 703 (1913) [CA **8**, 1763 (1914)].

<sup>13</sup> G. Plancher and B. Tanzi, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* [5] **23**, 11, 412 (1914) [CA **9**, 1477 (1915)].

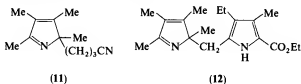
<sup>14</sup> K. Hess and F. Wissing, *Ber. Dtsch. Chem. Ges.* **47**, 1416 (1914) [CA **8**, 2706 (1914)].

<sup>15</sup> K. Hess, F. Wissing, and A. Suchier, *Ber. Dtsch. Chem. Ges.* **48**, 1865 (1915) [CA **10**, 465 (1916)].

uncertain as to whether they had the *2H*- or *3H*-isomer. One paper,<sup>14</sup> later corrected,<sup>15</sup> even suggested a dihydropyridine structure. Results apparently establishing a product as a *3H*-pyrrole (6),  $R^1 = R^3 = R^4 = \text{Me}$ ;  $R^2 = \text{H}$ ;  $R^5 = \text{Et}$ <sup>15</sup> were later reinterpreted in terms of *2H* structures.<sup>16</sup> *2H*-Pyrroles were characterized by ozonolysis, which gave, e.g., 2,3-butanedione rather than 3,3-dimethyl-2,4-pentanedione from pentamethylisopyrrole.<sup>16</sup> The UV spectra of the products from further methylation of *2H*-pyrroles and treatment with base are consistent with the chromophore in the methylene-pyrroline 3 (later<sup>17</sup> shown to be a mixture of 3 and 7), but not with the isomer 8.<sup>16</sup>



Evidence from NMR spectra also confirmed a *2H*-pyrrole structure, a diastereotopic methylene (\*) distinguishing between isomers 9 and 10.<sup>17</sup> These workers were unable to find any evidence of *3H*-pyrroles among the compounds isolated (but see Section III,B,1). It is interesting that all earlier workers associated a menthol- or camphor-like odor with products from the Grignard reaction,<sup>10,13-17</sup> since this is reported to be characteristic of the *3H* rather than the *2H* compounds.<sup>8</sup>



Mixed isomers (80%) can be obtained from tetrasubstituted pyrroles, the *3H* compound sometimes predominating.<sup>8</sup> The reaction has been used successfully with substituted alkyl halides in a search for routes to corrin intermediates, giving products such as 11 and 12, and in the preparation of *2H*-pyrroles for use in mechanistic studies on the thermal and photochemical rearrangements of *N*-substituted pyrroles.<sup>18-20</sup> Thus, the reaction of

<sup>16</sup> H. Booth, A. W. Johnson, E. Markham, and R. Price, *J. Chem. Soc.*, 1587 (1959).

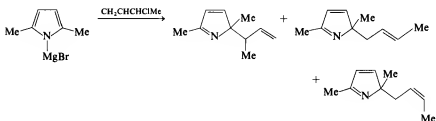
<sup>17</sup> H. Booth, A. W. Johnson, F. Johnson, and R. A. Langdale-Smith, *J. Chem. Soc.*, 650 (1963).

<sup>18</sup> J. M. Patterson and S. Soedigdo, *J. Org. Chem.* **33**, 2057 (1968).

<sup>19</sup> J. M. Patterson and L. T. Burka, *Tetrahedron Lett.*, 2215 (1969).

<sup>20</sup> J. M. Patterson, J. D. Ferry, and M. R. Boyd, *J. Am. Chem. Soc.* **95**, 4356 (1973).

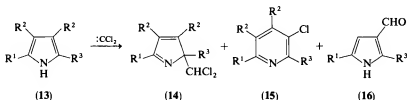
2,5-dimethylpyrrylmagnesium bromide with 3-chloro-1-butene gave a mixture of three isomeric products (Scheme 4), some of which were interconvertible under the conditions for isolation.<sup>20</sup> Pyrroles bearing an ester group<sup>16</sup> could not be alkylated, however, and halopyrroles failed to give the desired 2,2'-pyrryl-2*H* compounds.<sup>21</sup>



SCHEME 4

### 3. Dichlorocarbene

Plancher and co-workers described isopyrroles, believed to be the 2*H*-isomers (14), from the Reimer-Tiemann reaction with 2,5-dialkylpyrroles (13, R<sup>2</sup> = H).<sup>22,23</sup> Other products (15 and 16) were also formed (Scheme 5).



SCHEME 5

Later workers showed that the ratio of 2*H*-pyrrole to pyridine depended on the carbene source, the nature of the solvent, and the pH of the medium. Anhydrous neutral conditions (sodium trichloroacetate in dimethoxyethane) gave a high yield of 15 and a negligible amount of 14<sup>24,25</sup>; anhydrous basic

<sup>21</sup> H. Booth, A. W. Johnson, and F. Johnson, *J. Chem. Soc.*, 98 (1962).

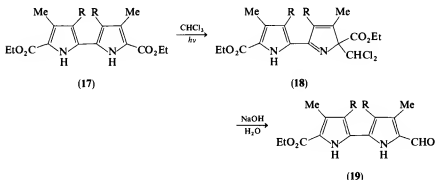
<sup>22</sup> G. Plancher and U. Ponti, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* [5] **18**, II, 469 (1909) [*CA* **4**, 2452 (1910)].

<sup>23</sup> G. Plancher and T. Zambonini, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* [5] **22**, II, 712 (1913) [*CA* **8**, 1764 (1914)].

<sup>24</sup> R. Nicoletti and M. Forcellese, *Gazz. Chim. Ital.* **95**, 83 (1965).

<sup>25</sup> R. L. Jones and C. W. Rees, *J. Chem. Soc. C*, 2249 (1969).

conditions (chloroform in ethanolic sodium ethoxide) gave low yields of both<sup>24,25</sup>; and aqueous basic conditions (chloroform in aqueous ethanolic potassium hydroxide) gave optimum yields of **14**.<sup>24</sup> The carbene has also been generated under phase-transfer conditions,<sup>26</sup> although these favor the pyridine (**15**) over the 2*H*-pyrrole (**14**), and recently by the action of sodium iodide on phenyltrichloromethylmercury.<sup>27,28</sup> The latter resulted in a mixture of six products, the yield of 2*H*-pyrroles being low.<sup>28</sup> When  $R^1 \neq R^3$ , two isomeric 3-chloropyridines (**15**)<sup>28,29</sup> and two aldehydes (**16**)<sup>29</sup> have been isolated, although in the examples studied ( $R^1 = t\text{-Bu}$ ) only one 2*H*-pyrrole (**13**) was found. Johnson *et al.* prepared the 2,2'-bipyrrole derivatives **18** ( $R = \text{Me, Et}$ ) (Scheme 6) from the diesters **17** in moderate yields using dichlorocarbene generated photochemically (for the first time) from chloroform.<sup>30</sup> The 2*H*-pyrroles **18** were later hydrolyzed to the aldehydes **19**, which were used in the synthesis of tetrapyrrolic compounds.<sup>30</sup>



SCHEME 6

The mechanism of this dichlorocarbene reaction has been thoroughly investigated. Plancher's claim to have converted 2*H*-pyrroles (**14**) to chloropyridines (**15**)<sup>22,23</sup> was shown to be inaccurate.<sup>31,32</sup> Although **14** could be

<sup>26</sup> F. De Angelis, A. Gambacorta, and R. Nicoletti, *Synthesis*, 798 (1976).

<sup>27</sup> A. Gambacorta, R. Nicoletti, S. Cerrini, W. Fedeli, and G. Gavuzzo, *Tetrahedron Lett.*, 2439 (1978).

<sup>28</sup> A. Gambacorta, R. Nicoletti, S. Cerrini, W. Fedeli, and G. Gavuzzo, *Tetrahedron* **36**, 1367 (1980).

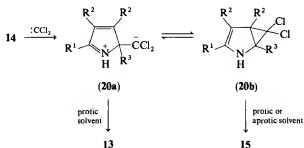
<sup>29</sup> R. Nicoletti, M. L. Forcelllese, and C. Germani, *Gazz. Chim. Ital.* **97**, 685 (1967).

<sup>30</sup> D. Dolphin, R. Grigg, A. W. Johnson, and J. Leng, *J. Chem. Soc.*, 1460 (1965).

<sup>31</sup> R. L. Jones, C. W. Rees, and C. E. Smithen, *Proc. Chem. Soc., London*, 217 (1964); R. L. Jones and C. W. Rees, *J. Chem. Soc. C*, 2255 (1969).

<sup>32</sup> R. Nicoletti and M. L. Forcelllese, *Tetrahedron Lett.*, 153 (1965); *Gazz. Chim. Ital.* **97**, 148 (1967).

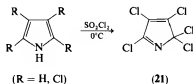
converted to a variety of other pyridines, including **15**,<sup>33</sup> with different bases, it was shown not to be an intermediate in the formation of **15** under the prevailing conditions. The major uncertainty has been whether **14** and **15** have a common precursor or are formed by independent routes, evidence having been produced both in support of<sup>33,34</sup> and against<sup>24,25</sup> a common intermediate. Recent evidence, however, strongly supports a common intermediate (**20a** in equilibrium with **20b**; Scheme 7), accounting for the dependence of product distribution on solvent proton donor capacity.<sup>28</sup>



SCHEME 7

#### 4. Halogenating Agents

Treatment of pyrrole or 2,3,4,5-tetrachloropyrrole with suluryl chloride gave pentachloro-2*H*-pyrrole (**21**, Scheme 8).<sup>35</sup> The same product had been obtained earlier from succinimide and phosphorus pentachloride (Section II,B,1,a).<sup>36</sup>



SCHEME 8

<sup>33</sup> R. Nicoletti and M. L. Forcellese, *Tetrahedron Lett.*, 3033 (1965); A. Gambacorta, R. Nicoletti, and M. L. Forcellese, *Tetrahedron* **27**, 985 (1971).

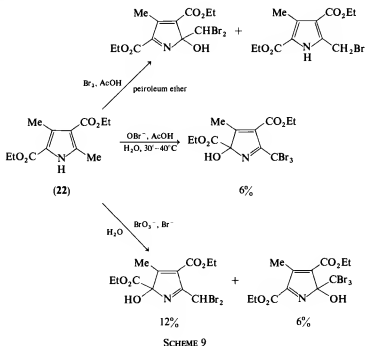
<sup>34</sup> M. L. Forcellese, A. Gambacorta, and R. Nicoletti, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* [8] **53**, 569 (1973) [*CA* **81**, 151202r (1974)].

<sup>35</sup> G. Mazzara, *Gazz. Chim. Ital.* **32**, II, 30, 33 (1902).

<sup>36</sup> R. Anschütz and G. Schroeter, *Justus Liebigs Ann. Chem.* **295**, 82 (1896).



Bromination of the pyrrole diester **22** gave various 2*H*-pyrroles in low yields, together with other compounds, depending on the conditions employed (Scheme 9).<sup>37,38</sup>



## 5. Oxidizing Agents

Preparations of isopyrroles by oxidation generally give rise to 2-hydroxy-2*H*-pyrrole derivatives and have been carried out almost exclusively using 2,3,4,5-tetraarylpyrroles. Exceptions have been the formation of 2,2'-bis-2*H*-pyrroles<sup>39</sup> and a 3*H*-pyrrole.<sup>40</sup> Oxidation has been attempted using a wide range of chemical oxidants, by photooxidation, and by electrochemical oxidation. The oxidation of monocyclic pyrroles was reviewed in 1973.<sup>3</sup>

a. *Chemical Oxidants.* In 1952, Kuhn and Kainer<sup>41</sup> reported that the oxidation of tetraphenylpyrrole (**23**, Scheme 10) in chloroform with lead

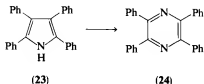
<sup>37</sup> A. Treibs and H. Bader, *Justus Liebigs Ann. Chem.* **627**, 182 (1959).

<sup>38</sup> A. Treibs and D. Grimm, *Justus Liebigs Ann. Chem.* **752**, 44 (1971).

<sup>39</sup> K. Tomita and N. Yoshida, *Tetrahedron Lett.*, 1169 (1971).

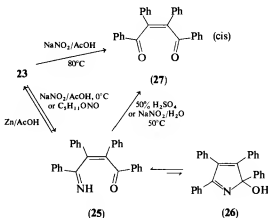
<sup>40</sup> V. Sprio, S. Petruso, L. Ceraulo, and L. Lamartina, *J. Heterocycl. Chem.* **14**, 797 (1977).

<sup>41</sup> von R. Kuhn and H. Kainer, *Justus Liebigs Ann. Chem.* **578**, 226, 227 (1952).



SCHEME 10

tetraacetate, lead dioxide, or perbenzoic acid led to moderate yields of the pyrazine **24**. They reported that reaction between **23** and either sodium nitrite in acetic acid or isoamyl nitrite gave a compound  $C_{28}H_{21}NO$ , isolable at low temperature, which had the imine structure **25** and existed in equilibrium with the 2*H*-pyrrole **26** (Scheme 11).<sup>41</sup> Both this compound and **24** were readily reconverted to pyrrole **23** with zinc and acetic acid.<sup>41</sup>



SCHEME 11

Later, Lutz and Boykin<sup>42</sup> showed that the product assigned structure **25** was in fact the 2*H*-pyrrole **26**. They also demonstrated that the *cis*-diketone **27** could be converted on treatment with ammonia to **26**, which in turn rearranged to the lactam **28** on heating with acid or base.<sup>42</sup> It is thus likely that the intermediate isolated in 1891 during the conversion of **27** to **28** with ammonia was also the 2*H*-pyrrole **26**.<sup>43</sup>

<sup>42</sup> R. E. Lutz and D. W. Boykin, D. W. Boykin, Jr., *J. Org. Chem.* **32**, 1179 (1967).

<sup>43</sup> F. Klingemann and W. F. Laycock, *J. Chem. Soc.* **59**, 140 (1891).



(28)



(29)



(30)

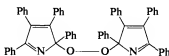


(31)

The pyrrole **23** was also oxidized to **26** using nitric acid, chromium(VI) oxide, lead tetraacetate in acetic acid, or phosphorus pentachloride in phosphorus oxychloride followed by hydrolysis in yields of up to 63%. However, hydrogen peroxide in acetic acid gave a mixture of the epoxy ketone **29** and the amide **30**; **29** was converted to **30** with ammonia, possibly via rearrangement of an intermediate (**31**).<sup>42</sup> Oxidation of the *N*-methyl derivative of **23** gave "pyrrolenineonium salts," which were difficult to purify.<sup>42</sup>



(32)



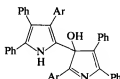
(33)



(34)



(35)



(36)

Lead dioxide in benzene converts **23** to the radical **32**, which reacts with oxygen to give a mixture of the diastereomers of the peroxide **33**.<sup>44,45</sup> Dibenzoylperoxide in benzene, however, converts **23** to the ester **34** in 53% yield via a mechanism thought not to involve addition of a benzoate radical.<sup>46</sup>

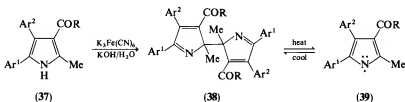
In contrast to **23**, 2,3,5-triarylpyrroles (**35**) were oxidized with potassium dichromate in acetic acid to give a mixture of products resulting from coupling of two pyrrole nuclei, one of which (4–6%) was the 3*H*-pyrrole derivative (**36**).<sup>40</sup> Mechanisms involving migration of the 5-aryl group are suggested for the formation of the various products.

<sup>44</sup> G. Rio, A. Ranjon, and O. Pouchot, *C. R. Hebd. Seances Acad. Sci., Ser. C* **263**, 634 (1966).

<sup>45</sup> G. Rio and M. J. Scholl, *Bull. Soc. Chim. Fr.*, 4676 (1968).

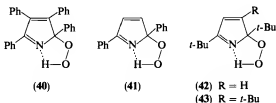
<sup>46</sup> R. Bonnett, P. Cornell, and A. F. McDonagh, *J. C. S. Perkin I*, 794 (1976).

Finally, ferricyanide oxidation of the tetrasubstituted pyrroles **37** (Scheme 12) under aqueous alkaline conditions gives high yields of the dimers **38**, which dissociate into radicals **39** on heating.<sup>39</sup>



SCHEME 12

b. *Photochemical Oxidation.* Rio and co-workers observed that the methylene blue-sensitized photochemical addition of oxygen to tetraphenylpyrrole (**23**) in dichloromethane, methanol, or carbon disulfide below room temperature gave 80–90% yields of the hydroperoxide **40**.<sup>44,47,48</sup> This compound behaved atypically in that on heating it dissociated to regenerate **23** (60%) and oxygen (together with 10% of the lactam **28**). Wasserman and Liberles<sup>49</sup> earlier carried out a similar oxygenation in methanol; they did not observe **40**, but the products isolated strongly suggested<sup>44</sup> that it was an intermediate (see Section IV,D,1). 2,5-Diphenylpyrrole was converted to **41** (50%), which was much less stable than its analog **40**.<sup>40</sup>



The only alkyl-substituted pyrroles that have been oxidized photochemically to isolable 2*H*-pyrroles are the 2,5-di-*tert*-butyl and the 2,3,5-tri-*tert*-butyl derivatives, which gave, respectively, the hydroperoxides **42** and **43**.<sup>50</sup> The absence of  $\alpha$ -hydrogen atoms on the ring substituents probably prevents major side reactions from taking place in these cases. Photooxidation of the

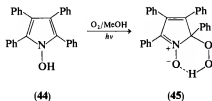
<sup>47</sup> C. Dufraisse, G. Rio, A. Ranjon, and O. Pouchot, *C. R. Hebd. Seances Acad. Sci., Ser. C* **261**, 3133 (1965).

<sup>48</sup> G. Rio, A. Ranjon, O. Pouchot, and M. J. Scholl, *Bull. Soc. Chim. Fr.*, 1667 (1969).

<sup>49</sup> H. H. Wasserman and A. Liberles, *J. Am. Chem. Soc.* **82**, 2086 (1960).

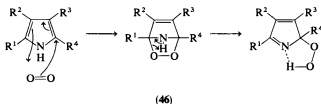
<sup>50</sup> R. Ramasseul and A. Rassat, *Tetrahedron Lett.*, 1337 (1972).

*N*-hydroxypyrrole **44** gives the analogous hydroperoxynitrone **45** (Scheme 13).<sup>51</sup>



SCHEME 13

Since singlet oxygen is a dienophile, such oxidations are believed to involve cycloaddition of oxygen to an endoperoxide (**46**, Scheme 14), followed by rearrangement to the hydroperoxide. Reduction in steric strain and the formation of a strong intramolecular hydrogen bond ( $\nu_{\max}$  2800  $\text{cm}^{-1}$ ) could provide the driving force in the second step.<sup>48</sup>



SCHEME 14

c. *Electrochemical Oxidation.* Libert, Caullet, and co-workers have investigated the electrochemical oxidation of a series of tetraarylpyrroles (**23** and **47**) using a rotating platinum microelectrode.<sup>52-55</sup> In aqueous methanol, 0.1 *M* in lithium perchlorate, 2-hydroxy-2*H*-pyrroles were isolated in high yields as their perchlorate salts (**48a**<sup>54</sup> and **48b**<sup>55</sup>) from **47a** and **47b**, respectively (Scheme 15). With **23**, however, no **48c** was observed; only the methoxy compound **49** was detected.<sup>53</sup> The difference in behavior was explained in terms of the stabilizing effect of the aryl *p*-substituent on the postulated intermediate monocation (see below).<sup>54</sup>

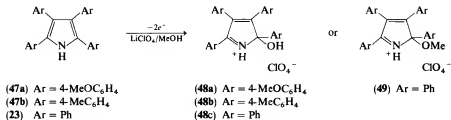
<sup>51</sup> G. Rio, A. Ranjon, and O. Pouchot, *Bull. Soc. Chim. Fr.*, 4679 (1968).

<sup>52</sup> M. Libert and C. Caullet, *Bull. Soc. Chim. Fr.*, 1947 (1971).

<sup>53</sup> M. Libert, C. Caullet, and S. Longchamp, *Bull. Soc. Chim. Fr.*, 2367 (1971).

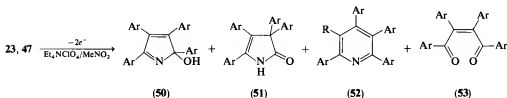
<sup>54</sup> M. Libert, C. Caullet, and J. Huguet, *Bull. Soc. Chim. Fr.*, 3639 (1972).

<sup>55</sup> M. Libert, C. Caullet, and G. Barbey, *Bull. Soc. Chim. Fr.*, 536 (1973).



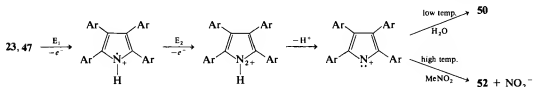
SCHEME 15

Oxidation in wet nitromethane, 0.1 *M* in tetraethylammonium perchlorate, gave up to four products (Scheme 16), the relative amounts of which depended on the temperature and the presence or absence of sodium carbonate.<sup>52-55</sup> At ~15°C the 2*H*-pyrrole **50** was the major product, but as the temperature was increased more pyridine (**52**, R = H) was formed, and at 90°C **50** could not be detected. Compounds **51** and **53** were also found at higher temperatures. Measurement of half-wave potentials relative to Ag/AgCl showed that the oxidation proceeded in two steps, values for each being 0.93 and 1.37 V for **47a**,<sup>54</sup> 1.08 and 1.69 V for **47b**,<sup>55</sup> and 1.17 and 1.77 V for **23**.<sup>53</sup> These reduction potentials correlate well with Taft  $\sigma^+$  constants.<sup>55</sup>



SCHEME 16

These and other data were interpreted in terms of the mechanism in Scheme 17. Product **51** was thought to arise from the thermal rearrangement of **50**, and the diketone **53** from reaction between **47**<sup>55</sup> (or possibly **50**<sup>42</sup>) and nitrite ion coproduced with **52**. That the additional carbon atom in the pyridine came from the solvent was confirmed by the isolation of **52** (R = D and

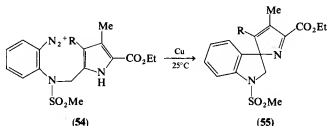


SCHEME 17

R = Me) from reactions carried out respectively, in deuteriated nitromethane and nitroethane.<sup>54</sup> A mechanism has been suggested.<sup>52</sup>

### 6. Miscellaneous

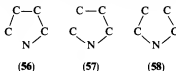
In the presence of copper, the diazonium salts **54** give the 2*H*-pyrroles **55** (Scheme 18) when R = COMe or CO<sub>2</sub>Et.<sup>56</sup> Successful cyclization apparently requires an electron-withdrawing group at the 3-position, for with **54** (R = Me) the reaction followed a different course. A spiro-2*H*-pyrrole related to **55** was prepared recently under conditions for the Fischer indole synthesis.<sup>56a</sup>



SCHEME 18

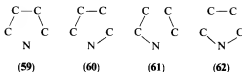
## B. BY CYCLIZATION OF OPEN-CHAIN COMPOUNDS

Isopyrrole rings have been assembled successfully by cyclization of each of the single chain fragments **56**–**58** and by combination of each of the two chain fragments **59**–**62**. The type **62** are 1,3-dipolar cycloadditions, using nitrile ylides, and are described in Section II,C. The remainder do not necessarily form distinct classes, since combination of two fragments can give a single chain intermediate, which is not isolated under the prevailing conditions before cyclizing to the isopyrrole. The classification of cyclizations made below is subject to this limitation. The tetrahedral carbon atom can be established either before or during the cyclization step.



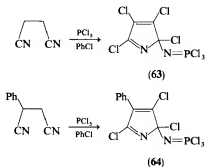
<sup>56</sup> S. Beveridge and J. L. Huppatz, *Aust. J. Chem.* **23**, 781 (1970); **25**, 1341 (1972).

<sup>56a</sup> H. von Dobeneck, E. Brunner, H. Bunke, G. Metzner, R. Schmidt, E. Weil, and J. Sonnenbichler, *Justus Liebig's Ann. Chem.*, 410 (1981).



### 1. Single Chain Fragments

a. *Succinic Acid Derivatives: Class 56.* Anschütz and Schroeter first demonstrated the preparation of pentachloro-2*H*-pyrrole (**21**) by the action of phosphorus pentachloride on succinimide or on dichloromaleimide.<sup>36</sup> This has become the method of choice for preparing this compound.<sup>57-59</sup> In a related reaction succinonitrile (or maleic or fumaric dinitriles) and its 2-phenyl analog may be converted to derivatives **63** and **64** or **21** (Scheme 19).<sup>60</sup> For **63** an incorrect structure was initially reported.<sup>61</sup> With less phosphorus pentachloride, 2-chloromaleonitrile was isolated; it is thought to be an intermediate in the formation of **63**.<sup>61</sup>



SCHEME 19

More highly substituted nitriles allow the isolation of the phosphorus-containing intermediates **65**, which are converted by aqueous base to amino-3*H*-pyrroles (**66**, Scheme 20) in high yields.<sup>62</sup>

<sup>57</sup> H. Ulrich, E. Kober, H. Schroeder, R. Rätz, and C. Grundmann, *J. Org. Chem.* **27**, 2585 (1962).

<sup>58</sup> C. M. Gladstone, P. H. Daniels, and J. L. Wong, *J. Org. Chem.* **42**, 1375 (1977).

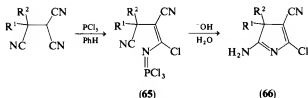
<sup>59</sup> R. Gompper and M. Junius, *Tetrahedron Lett.*, 2883 (1980).

<sup>60</sup> V. I. Shevchenko, V. P. Kukhar, A. A. Koval, and A. V. Kirsanov, *Zh. Obshch. Khim.* **38**, 1270 (1968) [*CA* **69**, 106391 (1968)].

<sup>61</sup> V. I. Shevchenko and V. P. Kukhar, *Zh. Obshch. Khim.* **36**, 735 (1966) [*CA* **65**, 8858 (1966)].

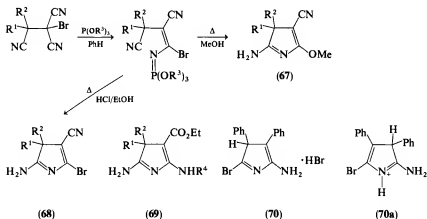
<sup>62</sup> V. I. Shevchenko and N. R. Litovchenko, *Dopov. Akad. Nauk Ukr. RSR, Ser. B: Geol., Geofiz., Khim. Biol.* **32**, 167 (1970) [*CA* **73**, 14406 (1970)]; V. I. Shevchenko, N. R. Litovchenko, and V. P. Kukhar, *Zh. Obshch. Khim.* **40**, 1229 (1970) [*CA* **74**, 76249 (1971)].





SCHEME 20

Foucaud and co-workers<sup>63</sup> have reported a related reaction using phosphite esters in place of phosphorus pentachloride and isolating amino-3H-pyrrole derivatives **67** and **68** (Scheme 21). A modification of the procedure led to diamino derivatives **69**.<sup>64</sup> The action of hydrogen bromide on 2,3-diphenylsuccinonitrile gave a salt formulated as **70** but in reality probably **70a**.<sup>65</sup>



SCHEME 21

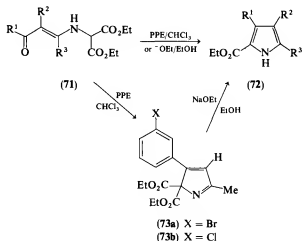
b. *Aminomalonate Derivatives: Classes 57 and 58.* As part of a study of the synthesis of analogs of the antifungal antibiotic pyrrolnitrin, a series of aminomalonate derivatives (**71**) were cyclized to 3-arylpyrroles

<sup>63</sup> R. Leblanc, E. Corre, and A. Foucaud, *Tetrahedron* **28**, 4039 (1972); M. Svalarich-Soenen and A. Foucaud, *ibid.*, 5149.

<sup>64</sup> R. Leblanc, E. Corre, M. Svalarich-Soenen, M. F. Chasle, and A. Foucaud, *Tetrahedron* **28**, 4431 (1972).

<sup>65</sup> L. G. Duquette and F. Johnson, *Tetrahedron* **23**, 4539 (1967).

(72,  $R^1 = \text{Ar}$ ) using either ethyl polyphosphate (PPE) in chloroform or sodium ethoxide in ethanol as the cyclizing agent (Scheme 22).<sup>66-68</sup> Under the former conditions, the 2*H*-pyrroles 73 were isolated and shown to be likely intermediates by their ready conversion to pyrroles of type 72 under basic conditions. In a related reaction, aminomalonate derivatives 71 ( $R^2 = \text{CO}_2-t\text{-Bu}$ ;  $R^3 = \text{Me}$ ) were cyclized successfully to the corresponding pyrroles 72 using zinc acetate in acetic acid as the cyclizing agent.<sup>69</sup> It seems likely that this reaction also proceeds via a 2*H*-pyrrole intermediate.



SCHEME 22

A class 58 cyclization on the aminocyanoacetate derivative 74 gave the pyrrolinone 75 (Scheme 23).<sup>70</sup> Alkylation occurred on the ring nitrogen, but acylation occurred at the carbonyl to give the 2*H*-pyrrole 76. The diester 75 was hydrolyzed to the acid 77 and cyclized to the 2*H*-pyrrolelactone 78, with spectroscopic properties similar to those of 76.

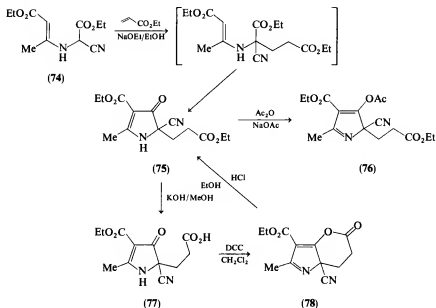
<sup>66</sup> S. Umio, K. Kariyone, K. Tanaka, and T. Kishimoto, *Chem. Pharm. Bull.* **17**, 576 (1969).

<sup>67</sup> S. Umio, K. Kariyone, K. Tanaka, T. Kishimoto, H. Nakamura, and M. Nishida, *Chem. Pharm. Bull.* **18**, 1414 (1970).

<sup>68</sup> S. Umio, K. Kariyone, K. Tanaka, T. Kishimoto, H. Naguchi, I. Ueda, and H. Nakamura, Belgian Patent 670,428 [*CA* **65**, 13661 (1966)]; Japanese Patent 16,131 (1968) [*CA* **70**, 57628 (1969)].

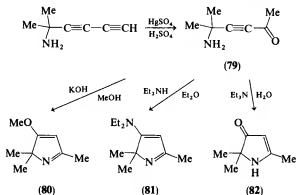
<sup>69</sup> H. Plieninger and H. Hussein, *Synthesis*, 587 (1970).

<sup>70</sup> T. Murata, T. Sugawara, and K. Ukawa, *Chem. Pharm. Bull.* **26**, 3080 (1978).



SCHEME 23

c. *Acetylene Derivatives: Classes 56 and 57.* The acetylenic amino ketone **79**, prepared by hydration of a diacetylene (Scheme 24), can be cyclized to 2H-pyrrole derivatives **80–82**.<sup>71</sup> Related diacetylenic compounds

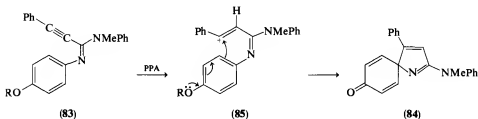


SCHEME 24

<sup>71</sup> B. P. Gusev, E. A. El'perina, and V. I. Kucherov, *Khim. Atsetilena, Tr. Vses. Konf., 3rd, 1968*, 26 (1972) [*CA* 79, 5220 (1973)]; *Khim. Geterotsikl. Soedin.* 7, 1530 (1971) [*CA* 77, 19497 (1972)].

were also converted to six-membered-ring oxygen and nitrogen heterocycles.<sup>71</sup>

Acetylenic imines (**83**, R = Me, Et) are cyclized by polyphosphoric acid (PPA) to the spiro-2*H*-pyrrole **84** (59–60%), together with two quinoline derivatives.<sup>72</sup> In the absence of the *p*-alkoxy group, only the quinolines are formed, suggesting an intermediate such as **85** in the formation of **84** (Scheme 25).

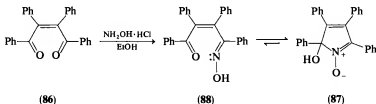


SCHEME 25

## 2. Combinations of Two Fragments

a. *1,4-Diketones and Amines: Class 59*. The reaction between the *cis*-diketone **27** (Scheme 11) and saturated ethanolic ammonia in a sealed tube gives the 2*H*-pyrrole **26** in high yield.<sup>43</sup> The structure of the product was confirmed in later applications.<sup>47,48</sup> Oxidation of tetraarylpyrroles,<sup>42</sup> however, remains the method of choice for compounds of type **50**.<sup>54,55</sup>

The reaction between the *cis*-diketone **86** and hydroxylamine was initially thought to give an isoxazole,<sup>73</sup> but Blatt showed the product to be the 2*H*-pyrrole *N*-oxide **87**,<sup>74</sup> formed via the oxime **88**, to which it was reconvered by conversion to the oxime anion and careful acidification (Scheme 26).<sup>75</sup>



SCHEME 26

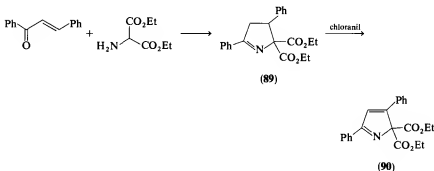
<sup>72</sup> W. Ried and R. Schweitzer, *Chem. Ber.* **109**, 1643 (1976).

<sup>73</sup> E. Oliveri-Mandala and E. Calderaro, *Gazz. Chim. Ital.* **44**, 85 (1914).

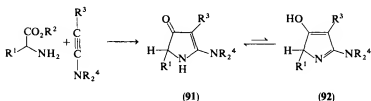
<sup>74</sup> A. H. Blatt, *J. Am. Chem. Soc.* **56**, 2774 (1934).

<sup>75</sup> A. H. Blatt, *J. Am. Chem. Soc.* **58**, 590 (1936).

b. *Miscellaneous: Classes 60 and 61.* Addition of diethyl aminomalonate to benzalacetophenene (Scheme 27) gives the pyrrole **89** (60%), which is readily oxidized to the 2*H*-pyrrole **90** (70%).<sup>76</sup> Amino acid esters react with 1-aminoacetylenes to give pyrrolinones **91**, which exist as such rather than as the hydroxy tautomers **92** (Scheme 28).<sup>77</sup>



SCHEME 27



SCHEME 28

A remarkable example of a stable 3*H*-pyrrole (**93**) with a hydrogen atom at C-3 was recently reported (Scheme 29). Large steric interactions between the 2- and 3-substituents evidently discourage isomerization to the 1*H*-pyrrole.<sup>78</sup> The NMR spectrum showed the side-chain methylene to be diastereotopic and part of an ABX system.

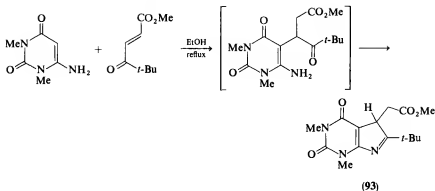
A diaminouracil was converted to the spiro-2*H*-pyrrole **94** (Scheme 30), a molecule of interest as a cholinesterase reactivator.<sup>79</sup> The structure was

<sup>76</sup> J. Koch, J.-F. Robert, and J. J. Panouse, *C. R. Hebd. Seances Acad. Sci., Ser. C* **286**, 95 (1978).

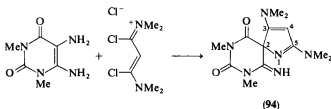
<sup>77</sup> R. Fuks and H. G. Viehe, *Tetrahedron* **25**, 5721 (1969).

<sup>78</sup> G. B. Bennett and R. B. Mason, *J. Org. Chem.* **42**, 1919 (1977).

<sup>79</sup> B. Kokel, H. G. Viehe, J. P. Declercq, G. Germain, and M. van Meerssche, *Tetrahedron Lett.*, 3799 (1980).

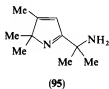


SCHEME 29



SCHEME 30

confirmed by X-ray crystallography.<sup>79,79a</sup> Finally, the 2*H*-pyrrole **95** was



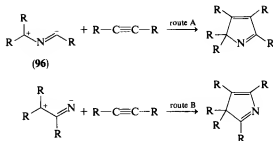
believed to be one of three products formed from 3-amino-3-methyl-2-butanone and potassium hydroxide.<sup>80</sup>

### C. BY 1,3-DIPOLAR CYCLOADDITIONS

2*H*-Pyrroles can be assembled by cycloaddition between a nitrile ylide (**96**) and an alkyne (Scheme 31, route A). An approach to 3*H*-pyrroles is

<sup>79a</sup> H. G. Viehe, personal communication.

<sup>80</sup> S. Gabriel, *Chem. Ber.* **44**, 57 (1911).



SCHEME 31

suggested by route B; although symmetry forbidden as a concerted process, the cycloaddition could work by a two-stage radical process.<sup>81</sup>

The 1,3-dipole **96** has been generated exclusively by thermal and photochemical ring-opening reactions of other heterocycles, both with and without elimination of another molecule. Precursor heterocyclic rings have been five-,<sup>82-89</sup> four-,<sup>90</sup> or three-membered.<sup>91-102</sup> Generally, the dipolarophile

<sup>81</sup> R. A. Firestone, *Tetrahedron* **33**, 3009 (1977).

<sup>82</sup> K. Burger and J. Fehn, *Angew. Chem., Int. Ed. Engl.* **10**, 728 (1971).

<sup>83</sup> K. Burger and J. Fehn, *Angew. Chem., Int. Ed. Engl.* **10**, 729 (1971); *Chem. Ber.* **105**, 3814 (1972).

<sup>84</sup> K. Burger and J. Fehn, *Tetrahedron Lett.*, 1263 (1972).

<sup>85</sup> K. Burger, W. D. Roth, and K. Neumayr, *Chem. Ber.* **109**, 1984 (1976).

<sup>86</sup> K. Burger and R. Ottlinger, *J. Fluorine Chem.* **12**, 519 (1978).

<sup>87</sup> K. Burger, R. Ottlinger, H. Goth, and J. Firl, *Chem. Ber.* **113**, 2699 (1980).

<sup>88</sup> W. Steglich, P. Gruber, H. U. Heininger, and F. Kneidl, *Chem. Ber.* **104**, 3816 (1971).

<sup>89</sup> J. Fischer and W. Steglich, *Angew. Chem., Int. Ed. Engl.* **18**, 167 (1979).

<sup>90</sup> K. Burger, W. Thenn, and E. Mueller, *Angew. Chem., Int. Ed. Engl.* **12**, 155 (1973).

<sup>91</sup> N. Gakis, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta* **57**, 1403 (1974).

<sup>92</sup> U. Widmer, N. Gakis, B. Arnet, H. Heimgartner, and H. Schmid, *Chimia* **30**, 453 (1976) [*CA* **86**, 89509 (1977)].

<sup>93</sup> W. Stegmann, P. Gilgen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta* **59**, 1018 (1976).

<sup>94</sup> N. Gakis, M. Märky, H.-J. Hansen, H. Heimgartner, H. Schmid, and W. E. Oberhänsli, *Helv. Chim. Acta* **59**, 2149 (1976).

<sup>95</sup> U. Gerber, H. Heimgartner, H. Schmid, and W. Heinzelmann, *Helv. Chim. Acta* **60**, 687 (1977).

<sup>96</sup> K. Isomura, M. Okada, and H. Taniguchi, *Chem. Lett.*, 629 (1972).

<sup>97</sup> A. Padwa, J. Smolanoff, and A. Tremper, *J. Am. Chem. Soc.* **97**, 4682 (1975).

<sup>98</sup> A. Padwa, J. Smolanoff, and A. Tremper, *J. Org. Chem.* **41**, 543 (1976).

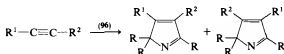
<sup>99</sup> A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.* **99**, 1514 (1977).

<sup>100</sup> A. Padwa and N. Kamigata, *J. Am. Chem. Soc.*, **99**, 1871 (1977).

<sup>101</sup> H. Hemetsberger, I. Spira, and W. Schaenfelder, *J. Chem. Res., Synop.*, 247; *J. Chem. Res., Miniprint*, 2701 (1977).

<sup>102</sup> K. Friedrich, G. Boeck, and H. Fritze, *Tetrahedron Lett.*, 3327 (1978).

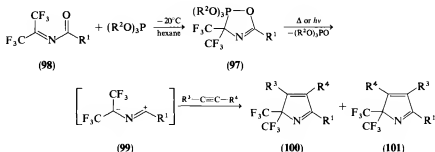
has been an alkyne, but alkenes which after cycloaddition lose a suitable leaving group to form the 2*H*-pyrrole have also been used.<sup>91-93</sup> In other cases intramolecular cyclization occurs.<sup>96-98,101,102</sup> Dimethyl acetylenedicarboxylate (DMAD) has been the most commonly used alkyne, but acetylene<sup>85</sup> and its mono-<sup>85</sup> and diphenyl<sup>82,83,85</sup> derivatives, methyl propiolate<sup>83,86,88,95</sup> and methyl phenylpropiolate,<sup>95</sup> can be used successfully. When the alkyne is unsymmetric, two regioisomeric products (Scheme 32) are observed. Product ratios seem to depend on a balance between steric and electronic factors<sup>83,85,86,88,95</sup>; orientation effects have been discussed for 1,3-dipolar cycloadditions both in terms of a concerted mechanism<sup>102a</sup> and a two-stage diradical mechanism.<sup>81</sup>



SCHEME 32

### 1. 1,3-Dipole from Five-Membered-Ring Heterocycles

a. *4,5-Dihydro-1,3,5-oxazaphosph(V)oles*. Burger and co-workers observed that oxazaphospholes (97), prepared from hexafluoroisopropylidenamides (98) and trialkyl phosphites (Scheme 33),<sup>83,103</sup> could be fragmented both thermally<sup>82,83,85</sup> and photochemically<sup>83,84</sup> to give a transient nitrile ylide (99). This in turn could be trapped by an alkyne to give for  $\text{R}^3 \neq \text{R}^4$  two isomeric 2*H*-pyrroles (100 and 101). Yields varied from 39% ( $\text{R}^1 = \text{R}^3 = \text{R}^4 = \text{Ph}$ ) to 81% ( $\text{R}^1 = t\text{-Bu}$ ;  $\text{R}^3 = \text{R}^4 = \text{H}$ ).<sup>85</sup> Isomer 101



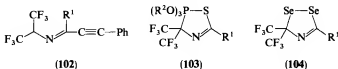
SCHEME 33

<sup>102a</sup> R. Huisgen, *J. Org. Chem.* **41**, 403 (1976).

<sup>103</sup> K. Burger, J. Fehn, and E. Moll, *Chem. Ber.* **104**, 1826 (1971).



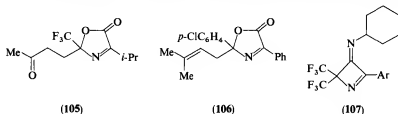
predominated for  $R^1 = t\text{-Bu}$  and  $R^3 = \text{H}$ ,<sup>83,85</sup> but for  $R^1 = \text{Ar}$ ,  $R^3 = \text{H}$ , and  $R^4 = \text{Ph}$  isomers **100** and **101** were formed equally and a third product (**102**)



was isolated. The ratio of products was not affected by the nature of the *p*-substituent on  $R^1$ .<sup>85</sup>

b. *Related Heterocycles.* The ylide **99** was also prepared successfully by thermolysis of the sulfur- (**103**)<sup>86</sup> and selenium-containing (**104**)<sup>87</sup> systems and trapped with alkynes to give **100** and **101**.

c. *2H-Oxazolones.* Nitrile ylides have also been generated by pyrolysis of the oxazolones **105**<sup>88</sup> and **106**<sup>89</sup> and trapped with alkynoic esters to give



2*H*-pyrroles. The ylide generated from **106** behaved as a spin-paired diradical species in an intramolecular insertion reaction.<sup>89</sup>

## 2. 1,3-Dipole from Four-Membered-Ring Heterocycles

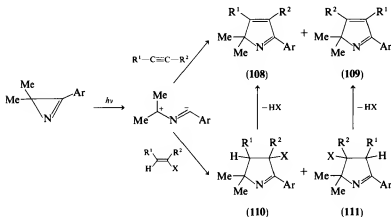
Photolysis of the iminoazete **107** in the presence of DMAD gives 2*H*-pyrroles **100** ( $R^1 = \text{Ar}$ ;  $R^3 = R^4 = \text{CO}_2\text{Me}$ ).<sup>90</sup> Presumably, the other product is cyclohexylisonitrile.

## 3. 1,3-Dipole from Three-Membered-Ring Heterocycles

a. *Azirines with External Dipolarophile.* Irradiation (high-pressure Hg lamp) of azirines at the wavelength of the  $n \rightarrow \pi^*$  transition causes fragmentation to 1,3-dipoles,<sup>104</sup> which have been identified by UV spectroscopy

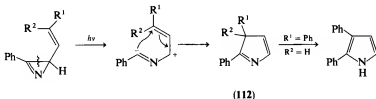
<sup>104</sup> A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.* **95**, 1945 (1973).

in a 2-methylpentane glass at  $-185^{\circ}\text{C}$ .<sup>95</sup> 2*H*-Pyrroles **108** and **109** (Scheme 34) are formed directly with alkynes<sup>95,99,100</sup> or indirectly via **110** or **111** with polar alkenes, followed by elimination.<sup>91-93</sup> In one case, the 1,3-dipoles were trapped with carbon dioxide to give oxazolones analogous to **105** and **106** and then fragmented once more photochemically to give 2*H*-pyrroles with DMAD.<sup>94</sup> Polar alkenes add with high regioselectivity,<sup>91-93</sup> which is independent of the nature of the aryl *p*-substituent,<sup>95</sup> giving essentially one isomer (**108** or **109**) and thus offering a more attractive route to single-isomer 2*H*-pyrroles than the less regioselective alkynes.<sup>95</sup> Yields have ranged from 26 to 80%.



SCHEME 34

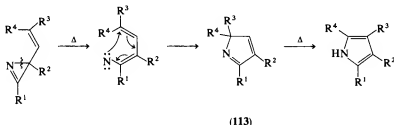
b. *Intramolecular Cyclizations via Azirenes.* Nitrile ylides generated photochemically from azirenes do not appear to have been added intramolecularly to alkynes. However, derivatives of 3-vinylazirine are transformed, apparently via 3*H*-pyrroles (**112**) to 1*H*-pyrroles (Scheme 35).<sup>97,98</sup> Attempts to isolate **112** by having  $\text{R}^1, \text{R}^2 \neq \text{H}$  resulted only in side reactions.<sup>98</sup> When



SCHEME 35

the double bond was farther along the side chain, different ring systems were formed, suggesting that the ylide had carbene character.<sup>100,101</sup>

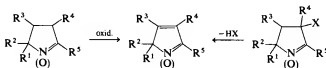
In contrast, thermolysis of 3-vinylazirines led to 2*H*-pyrroles (113) in good yields through cyclization of an intermediate nitrene (Scheme 36)<sup>96,101,102</sup>; in some cases, under the prevailing high temperatures, these rearranged to 1*H*-pyrroles via [1,5]-shifts.<sup>98,102</sup>



SCHEME 36

#### D. FROM 1-PYRROLINES

1-Pyrrolines and their *N*-oxides have been converted to 2*H*-pyrroles (and their *N*-oxides), both by oxidation and by elimination (Scheme 37). 1-Pyrroline *N*-oxides have generally been prepared by Michael addition of a 2-nitroalkane anion to an  $\alpha,\beta$ -unsaturated ketone followed by reductive cyclization<sup>104a-108</sup>; a modified approach was used for the 5-cyano compounds.<sup>104a,108a</sup> Cycloaddition reactions between nitrile ylides and alkenes



SCHEME 37

<sup>104a</sup> R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 2094 (1959).

<sup>105</sup> D. J. Fry, B. A. Lea, and J. D. Kendall, British Patent 906,802 [*CA* **60**, 11987 (1964)]; British Patent 906,803 [*CA* **60**, 11988 (1964)].

<sup>106</sup> D. St. C. Black and N. A. Blackman, *Aust. J. Chem.*, **32**, 1795 (1979).

<sup>107</sup> H. Bender and D. Döpp, *Tetrahedron Lett.*, 1833 (1980).

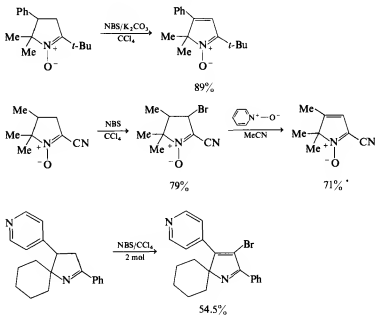
<sup>108</sup> K.-H. Pfoertner and J. Foricher, *Helv. Chim. Acta* **63**, 658 (1980).

<sup>108a</sup> D. St. C. Black, V. M. Clark, R. S. Thakur, and Lord Todd, *J. C. S., Perkin I*, 1951 (1976); D. St. C. Black, N. A. Blackman, and A. B. Boscacci, *Aust. J. Chem.*, **32**, 1775 (1979).

constitute the preferred method for preparing 1-pyrrolines,<sup>82-86,91-93,109</sup> although other methods have been used.<sup>76,105</sup>

### 1. Oxidations

a. *With N-Bromosuccinimide.* 1-Pyrrolines or their *N*-oxides with *N*-bromosuccinimide (NBS) in carbon tetrachloride can give 2*H*-pyrroles<sup>83,106,108</sup> or bromo-substituted derivatives,<sup>106,108</sup> depending on the ring substituents and the amount of NBS used. The intermediate bromopyrroline (Scheme 38) has been isolated in some cases.<sup>108,110</sup>

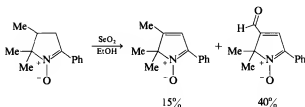


SCHEME 38

b. *Other Oxidizing Agents.* Chloranil has been mentioned earlier (Section II.B.2.b; Scheme 27)<sup>76</sup>; dioxane dibromide has been used to prepare a 3,4-dibromo-2*H*-pyrrole *N*-oxide in 26% yield.<sup>106</sup> Selenium dioxide in ethanol is also effective, giving yields of up to 75%, but when a 3-methyl group is present side-chain oxidation also occurs (Scheme 39).<sup>107</sup>

<sup>109</sup> L. Aepli, K. Bernauer, F. Schneider, K. Strub, W. E. Oberhansli, and K.-H. Pfoertner, *Helv. Chim. Acta* **63**, 630 (1980); K.-H. Pfoertner and R. Zell, *ibid.*, 645.

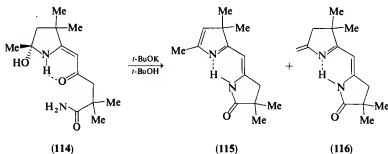
<sup>110</sup> D. St. C. Black, N. A. Blackman, and R. F. C. Brown, *Tetrahedron Lett.*, 3423 (1975); *Aust. J. Chem.* **32**, 1785 (1979).



SCHEME 39

## 2. Eliminations

a. *Loss of Water.* 3-Hydroxy-1-pyrrolines, prepared by rearrangement of *N*-oxides with acetic anhydride,<sup>105</sup> hydrolysis of 3-bromo-1-pyrrolines,<sup>110</sup> or Grignard addition to *N*-oxides of 1-pyrroline-3-ones,<sup>111</sup> undergo acid-catalyzed dehydration to 2*H*-pyrroles in high yields. However, for certain ring substituents an isomer with an exocyclic double bond may be formed.<sup>111</sup> Dehydration of the pyrrolidine derivative **114** with strong base gave a rare example of a 3*H*-pyrrole (**115**), together with the isomer (**116**) (Scheme 40) in a ratio of 3.5:1 (90%).<sup>112</sup>

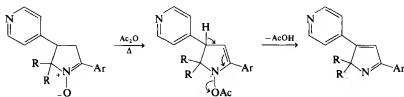


SCHEME 40

b. *Others.* Eliminations from the 1-pyrroline products of cycloadditions between nitrile ylides and polar alkenes have been referred to above (Section II,C,3,a).<sup>91-93</sup> Conversion of 1-pyrroline *N*-oxides to 2*H*-pyrroles with acetic anhydride has been achieved<sup>108</sup> by a mechanism different from that suggested in ref. 105 (Scheme 41).

<sup>111</sup> D. St. C. Black, N. A. Blackman, and L. M. Johnstone, *Aust. J. Chem.* **32**, 2025 (1979).

<sup>112</sup> R. V. Stevens, L. E. DuPree, Jr., W. L. Edmonson, L. L. Magid, and M. P. Wentland, *J. Am. Chem. Soc.* **93**, 6637 (1971).

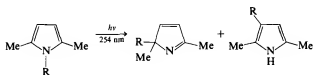


SCHEME 41

## E. OTHER METHODS

1. *By Rearrangement of N-Alkylpyrroles*

Patterson and co-workers<sup>113</sup> observed that the thermal rearrangement of *N*-alkylpyrroles led to a mixture of 2- and 3-alkyl derivatives and suggested that a 2*H*-pyrrole was an intermediate. Photolysis of the same class of compounds, using a low-pressure Hg lamp, led to isolable 2*H*-pyrroles as well as 3-alkylpyrroles (Scheme 42).<sup>19,20</sup> A chiral group migrates with some retention of optical activity,<sup>19</sup> and an *N*-( $\alpha$ -methallyl) derivative gave a mixture of  $\alpha$ -methallyl and *cis*- and *trans*-crotyl products.<sup>20</sup> The 3-isomer appears to arise from a direct [1,3]-shift rather than via the 2*H*-pyrrole.<sup>20</sup>



SCHEME 42

2. *From Carbanion Addition to Azirines*

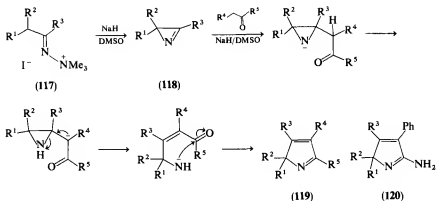
Hydrazonium salts (117) with sodium hydride in DMSO give azirines (118), which react further with ketones to give 2*H*-pyrroles (119); benzyl cyanide similarly gives 120 (Scheme 43).<sup>114–116</sup> This reaction is claimed to be the most convenient general route to 2*H*-pyrroles (yields 20–80%).<sup>114</sup>

<sup>113</sup> J. M. Patterson, L. T. Burka, and M. R. Boyd, *J. Org. Chem.* **33**, 4033 (1968).

<sup>114</sup> A. Laurent, P. Mison, A. Nafti, and N. Pellissier, *Tetrahedron Lett.*, 4511 (1978); *Tetrahedron* **35**, 2285 (1979).

<sup>115</sup> A. Laurent, P. Mison, A. Nafti, and N. Pellissier, *Tetrahedron Lett.*, 1587 (1979).

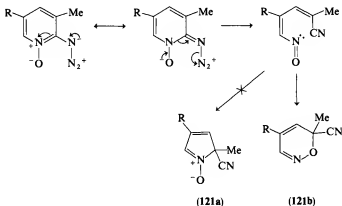
<sup>116</sup> A. Padwa and Y. Kulkarni, *Tetrahedron Lett.*, 107 (1979).



SCHEME 43

### 3. From 2-Azidopyridine *N*-Oxides

Thermolysis of 3-substituted 2-azidopyridine *N*-oxides at 90°C was originally thought to give 2*H*-pyrrole *N*-oxides (121a, 80–90%, Scheme 44).<sup>117</sup> However, the product was recently shown to be the isomeric oxazoline 121b.<sup>117a</sup>



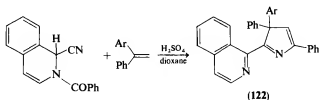
SCHEME 44

<sup>117</sup> R. A. Abramovitch and B. W. Cue, *Heterocycles* **2**, 297 (1974); *J. Am. Chem. Soc.* **98**, 1478 (1976).

<sup>117a</sup> R. A. Abramovitch and C. Dupuy, *J. C. S. Chem. Commun.*, 36 (1981).

4. 3*H*-Pyrroles from Reissert Compounds

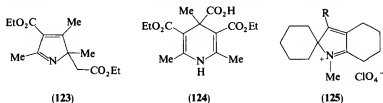
Isoquinoline Reissert compounds react with 1,1-diarylethenes in the presence of acid to give 3*H*-pyrroles (**122**, Scheme 45).<sup>6,118</sup> The mechanism of related reactions has been discussed in detail.<sup>118a</sup>



SCHEME 45

## 5. Miscellaneous

The 2*H*-pyrrole **123** (65%) was formed, together with a pyridine and other 1*H*-pyrrole products, on pyrolysis of the dihydropyridine **124**. No other



dihydropyridines studied gave a 2*H*-pyrrole.<sup>119</sup> The pyrrolinium salts **125** resulted from treatment of 2-pyrrolin-3-ones with alkylolithiums followed by perchloric acid.<sup>120</sup> Both 2*H*-pyrrole<sup>121,121a</sup> and 3*H*-pyrrole<sup>122</sup> units are found in some synthetic dehydrocorrins, and 3*H*-pyrrole units are found in some corphins and their derivatives.<sup>123</sup>

<sup>118</sup> W. E. McEwen, D. H. Berkebile, T. K. Liao, and Y. S. Lin, *J. Org. Chem.* **36**, 1459 (1971).

<sup>118a</sup> W. E. McEwen, M. A. Hernandez, C. F. Ling, E. Marmugi, R. M. Padronaggio, C. M. Zepp, and J. J. Lubinkowski, *J. Org. Chem.* **46**, 1656 (1981).

<sup>119</sup> J. F. Biellmann and H. J. Callot, *Tetrahedron* **26**, 4809 (1970).

<sup>120</sup> A. I. Meyers and S. Singh, *Tetrahedron* **25**, 4161 (1969).

<sup>121</sup> D. Dolphin, R. L. N. Harris, J. L. Huppatz, A. W. Johnson, and I. T. Kay, *J. Chem. Soc. C*, 30 (1966); R. Grigg, A. W. Johnson, R. Kenyon, V. B. Math, and K. Richardson, *ibid.*, 176 (1969).

<sup>121a</sup> C. Angst, C. Kratky, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.* **20**, 263 (1981).

<sup>122</sup> R. Grigg, A. W. Johnson, K. Richardson, and K. W. Shelton, *J. Chem. Soc. C*, 655 (1969).

<sup>123</sup> A. Eschenmoser, A. P. Johnson, P. Wehrli, and R. Fletcher, *Angew. Chem., Int. Ed. Engl.* **7**, 623 (1968).

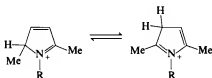


### III. Structure and Physical Properties

#### A. STRUCTURE

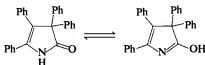
##### 1. Tautomerism

a. *Between 1H-, 2H-, and 3H-Pyrroles.* Except for **93**, mentioned below, no evidence has been found for the existence of 2H- and 3H-tautomers in equilibrium with simple 1H-pyrroles.<sup>123a</sup> Indeed, recent MINDO/3 calculations estimate 2H-pyrroles unsubstituted at the 2-position to be 70–80 kJ mol<sup>-1</sup> higher in energy than their 1H-tautomers, the difference increasing to about 110 kJ mol<sup>-1</sup> when a 2-methyl group is present.<sup>124</sup> A 3H-pyrrole containing a 3-hydrogen (**93**, Scheme 29) has been isolated when steric constraints apparently raise the energy of the 1H-tautomer considerably.<sup>78</sup> With fully alkylated isopyrroles, the 3H form has been shown to be thermodynamically unstable relative to the 2H-isomer.<sup>7</sup> Protonated pyrroles exist in strong acid solution as tautomeric mixtures of 2H- and 3H-pyrrolium salts (Scheme 46), some substituents favoring the 3H-isomer.<sup>125</sup>



SCHEME 46

b. *Between Hydroxypyrroles and Pyrrolones.* Spectroscopic support has been claimed for tautomeric equilibria involving both 3-hydroxy-2H-pyrroles (Scheme 28)<sup>77</sup> and 2-hydroxy-3H-pyrroles (Scheme 47)<sup>126</sup> with their oxo forms.



SCHEME 47

<sup>123a</sup> J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, "The Tautomerism of Heterocycles," *Adv. Heterocycl. Chem.*, Suppl. 1, p. 215. Academic Press, New York, 1976.

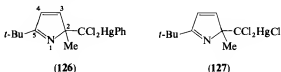
<sup>124</sup> A. Karpfen, P. Schuster, and H. Berner, *J. Org. Chem.* **44**, 374 (1979).

<sup>125</sup> E. B. Whipple, Y. Chiang, and R. L. Hinman, *J. Am. Chem. Soc.* **85**, 26 (1963); R. L. Hinman and S. Theodoropoulos, *J. Org. Chem.* **28**, 3052 (1963); Y. Chiang, R. L. Hinman, S. Theodoropoulos, and E. B. Whipple, *Tetrahedron* **23**, 745 (1967).

<sup>126</sup> J. Y. Guyon, M. Libert, and C. Caillet, *J. Chem. Res., Synop.*, 202; *J. Chem. Res., Miniprint*, 2582 (1978).

## 2. Bond Lengths and Angles

The X-ray crystal and molecular structures have been determined for three 2*H*-pyrrole derivatives; namely, **94**,<sup>79,79a</sup> **126**, and **127**,<sup>27</sup> two independent molecules of structure **127** coexisting in the unit cell. Bond lengths and angles are summarized in Table I for structures **94** and **126**, data for the



former revealing the electron-donating effect of the dimethylamino groups in the increased N-1—C-5 and C-3—C-4 and the decreased C-4—C-5 bond lengths. The smaller C-2—N-1—C-5 angle in **94** also probably reflects the greater *p*-character of the N-1—C-5 bond.

TABLE I  
BOND PARAMETERS<sup>a</sup> FOR 2*H*-  
PYRROLES **94**<sup>79a</sup> AND **126**<sup>27</sup>

Parameter	<b>94</b>	<b>126</b>
Bonds length (Å)		
N-1—C-2	1.475 (23)	1.46 (2)
N-1—C-5	1.364 (30)	1.29 (2)
C-2—C-3	1.514 (25)	1.50 (2)
C-3—C-4	1.390 (33)	1.35 (2)
C-4—C-5	1.476 (26)	1.49 (2)
Bond angle (deg)		
C-2—N-1—C-5	105.4 (16)	107.3 (11)
N-1—C-2—C-3	107.6 (14)	106.2 (11)
C-2—C-3—C-4	107.1 (17)	107.5 (14)
C-3—C-4—C-5	106.6 (19)	106.2 (13)
N-1—C-5—C-4	113.0 (19)	112.9 (13)

<sup>a</sup> Ring numbering is as indicated on structures **94** and **126**; standard deviations are given in parentheses.

## B. SPECTROSCOPIC PROPERTIES

## 1. Ultraviolet Spectra

2,2,5-Trialkyl-2*H*-pyrroles absorb between 210 and 225 nm (ethanol, log  $\epsilon$  3.5–3.6).<sup>19–21</sup> A 5-phenyl substituent gives a bathochromic shift to 244 nm (log  $\epsilon$  4.10)<sup>92</sup>; additional alkyl or phenyl groups in the 4- and/or

3-positions have little extra effect.<sup>92,114</sup> 2,2,3,5-Tetraalkyl- and 2,2,3,4,5-pentaalkyl-2*H*-pyrroles<sup>8,16,21</sup> absorb near 240 nm ( $\log \epsilon$  3.5) in ethanol and near 255–265 nm ( $\log \epsilon$  3.7) in acid.<sup>8,16</sup> The 3*H* analogs, the 2,3,3,4-tetraalkyl- and 2,3,3,4,5-pentaalkylpyrroles, have longer-wavelength absorption, between 255 and 265 nm ( $\log \epsilon$  3.4) in ethanol and 270–285 nm ( $\log \epsilon$  3.4) in acid.<sup>8</sup> These data suggest that the product formulated by Johnson and co-workers<sup>16</sup> as 3-ethyl-2,2,4-trimethyl-2*H*-pyrrole might be the isomeric 3*H* compound. 2,5-Dimethylpyrroles protonated at C-3 show absorption  $\sim 40$  nm to longer wavelength relative to the C-2 protonated forms,<sup>125</sup> consistent with the above. The effect of conjugating ester groups<sup>94,95,100,119</sup> or of electron-donating groups<sup>71</sup> is less clear. 2,2,3,4,5-Pentachloro-2*H*-pyrrole shows maxima at 220 and 282 nm ( $\log \epsilon$  3.5 and 3.0).<sup>127</sup> Figures quoted as 284 nm for a pentaalkyl-2*H*-pyrrole<sup>25</sup> and as 287.5 nm for a phenyl(trialkyl)-2*H*-pyrrole<sup>114</sup> seem to be in error. In the spectra of 2*H*-pyrrole *N*-oxides, a band is found near 300 nm ( $\log \epsilon$  3.7),<sup>111</sup> which moves to longer wavelengths and is accompanied by a second short-wavelength band when a conjugating substituent is introduced at C-5.<sup>106,110,111</sup>

## 2. Infrared Spectra

A peak in the range 1660–1610  $\text{cm}^{-1}$  has been assigned to  $\nu_{\text{C}=\text{N}}$  in a wide range of 2*H*-pyrroles.<sup>8,19,20,25,50,71,83,85,95,114</sup> A second band between 1570 and 1520  $\text{cm}^{-1}$  seems to be associated with  $\nu_{\text{C}=\text{C}}$ .<sup>8,25,50,71,127</sup> A third near 1350  $\text{cm}^{-1}$ , reported in the spectra of several 2*H*-pyrroles,<sup>114</sup> was assigned by one group<sup>25</sup> to  $\nu_{\text{C}-\text{N}}$ . The two 3*H*-pyrroles for which there are data<sup>8</sup> absorb at 1650 and 1580  $\text{cm}^{-1}$ .

*N*-Oxides having no conjugating substituents show only weak absorption between 1605 and 1560  $\text{cm}^{-1}$ ,<sup>106,110,111</sup> this presumably arising from  $\nu_{\text{C}=\text{C}}$ . A common intense absorption, found in the range 1300–1220  $\text{cm}^{-1}$ ,<sup>106,110,111</sup> possibly arises from the nitrone fragment. A band at 1525  $\text{cm}^{-1}$  so assigned to structure **121a**<sup>117</sup> was in error.<sup>117a</sup> A peak near 2800  $\text{cm}^{-1}$  has been used to diagnose the intramolecular hydrogen bond in the hydroperoxides **40–43** and **45**.<sup>47–51</sup>

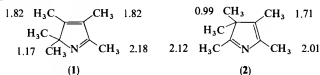
## 3. <sup>1</sup>H Nuclear Magnetic Resonance Spectra

Most papers after 1965 describing isopyrroles give <sup>1</sup>H NMR spectral assignments, so only general data for ring hydrogen atoms and methyl substituents are discussed here. Solvents have generally been CDCl<sub>3</sub> or CCl<sub>4</sub>. No 2*H*-pyrroles with a proton at C-2 have been reported except

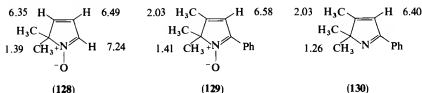
<sup>127</sup> C. M. Gladstone and J. L. Wong, *J. Agric. Food Chem.* **25**, 489 (1977).

salts<sup>5a</sup>: *gem*-dimethyl groups give signals in the range  $\delta$  1.2–1.6 (tetramethylsilane at  $\delta$  0.0). Protons at C-3 ( $\delta$  7.0–7.9) generally absorb to lower field than those attached at C-4 ( $\delta$  5.9–7.3), this being particularly apparent in molecules unsubstituted at both positions, where coupling ( $^3J_{HH} = 5$  Hz) is also observed.<sup>18,19,25,28,50,85,92,101,102</sup> The response of these chemical shifts to the nature of ring substituents parallels the electron-withdrawing or electron-releasing properties of the substituents. Methyl groups at C-3 and C-4 fall in the range  $\delta$  1.7–2.0, the former showing coupling with a proton ( $^4J_{HH} = 1.5$ –2.0 Hz)<sup>92,114</sup> or another methyl ( $^5J_{HH} = 1.2$  Hz)<sup>25</sup> at C-4. Proton NMR spectra have apparently not yet been published for 2*H*-pyrroles unsubstituted at C-5, but methyl groups at this position appear between  $\delta$  2.0 and 2.4<sup>8,18,19,25,66,119</sup> and, exceptionally, as high as  $\delta$  2.6.<sup>70</sup> Coupling with a proton at C-4 has also been observed.<sup>19</sup>

Data have been recorded for one 3*H*-pyrrole with a proton at C-3 ( $\delta$  3.39)<sup>78</sup> and one with a proton at C-5 ( $\delta$  6.64)<sup>8</sup>; chemical shifts for the two isomeric pentamethylisopyrroles **1** and **2** are shown. Methylene groups at the tetrahedral ring carbon atom are diastereotopic, and this fact has aided in structural assignments.<sup>8,17,78,119</sup>



Data have been recorded for a wide variety of 2*H*-pyrrole *N*-oxides,<sup>106,107,110,111,117</sup> those for the simplest (**128**) being shown and having  $^3J_{3,4} = 6.6$ ,  $^4J_{3,5} = 1.2$ , and  $^3J_{4,5} = 1.0$  Hz.<sup>107</sup> The effect of the *N*-oxide group is seen by comparing structures **129** ( $^4J_{HH} = 1.5$  Hz)<sup>107</sup> and **130** ( $^4J_{HH} = 1.4$  Hz),<sup>92</sup> both in  $\text{CDCl}_3$ ; the C-2 methyl signals are shifted to  $\delta$  1.6–1.7 by a C-3 phenyl group.



#### 4. $^{13}\text{C}$ Nuclear Magnetic Resonance Spectra

Several papers report  $^{13}\text{C}$  NMR spectra (tetramethylsilane at  $\delta$  0.0) for 2*H*-pyrroles.<sup>72,79,92,93,114,127</sup> The tetrahedral carbon atom (C-2) appears in the range  $\delta$  78–82 when carrying two methyl groups ( $\delta$  98.33 in the penta-chloro compound<sup>127</sup>), the methyl groups giving a signal between  $\delta$  23 and 24.

Ranges for C-3, C-4, and C-5 are, respectively,  $\delta$  162–173 (except when substituted with CN<sup>93</sup>),  $\delta$  118–121 when unsubstituted (near  $\delta$  135 when alkyl-substituted), and  $\delta$  166–178. Methyl groups at C-3 and C-4 appear between  $\delta$  11 and 13.5.<sup>92,114</sup> Data have not apparently been published for *N*-oxides or for 3*H*-pyrroles.

### 5. <sup>19</sup>F Nuclear Magnetic Resonance Spectra

The <sup>19</sup>F NMR spectra of compounds **100** measured in CDCl<sub>3</sub> (relative to external trifluoroacetic acid) show a signal in the range –8.8 to –9.4 ppm when R<sup>3</sup> = H<sup>85</sup> and between –10.9 and –11.8 ppm in other cases.<sup>85,87</sup> Long-range coupling is observable with a proton at C-4 (R<sup>4</sup> = H).<sup>85</sup>

### 6. Mass Spectra

Although mass spectra of many 2*H*-pyrroles<sup>28,92–95,108,114,119</sup> and some *N*-oxides<sup>107,110,111</sup> have been reported rather fully, the fragmentation pattern for only one<sup>119</sup> appears to have been analyzed. In all examples reported the parent ion is very prominent and is often the base peak.

## C. BASICITY

Isopyrroles are very much more basic than 1*H*-pyrroles, this property permitting their facile separation from the latter.<sup>8–10,13–18,21</sup> Measurements of p*K*<sub>a</sub> do not appear to have been made. Salts of 2*H*-pyrroles have been isolated by treatment of the bases with strong acid<sup>10,42,44,77</sup> and by alkylation at nitrogen,<sup>16,17,119</sup> as well as by indirect methods.<sup>5a,55,120</sup>

## IV. Reactions of 2*H*- and 3*H*-Pyrroles

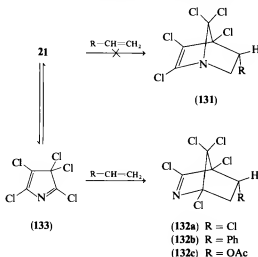
### A. ADDITIONS TO THE RING

#### 1. Hydrogen

Sodium in ethanol has been used to reduce a 2*H*-pyrrole to the pyrrolidine,<sup>9,16</sup> as has catalytic hydrogenation using platinum oxide.<sup>96</sup> The latter method, however, took compound **80** only to the 3-pyrroline, as did sodium borohydride.<sup>71</sup> Sodium borohydride reduction of the methiodide salt of **123** also gave a 3-pyrroline.<sup>119</sup>

## 2. Cycloadditions

a. *Diels-Alder Additions*. Isopyrroles are azadienes and might be expected to react with alkenes or alkynes with formation of a six-membered ring. Wong and co-workers successfully formed adducts between the pentachloro compound **21** and norbornadiene,<sup>58,127,128</sup> cyclopentadiene,<sup>128,129</sup> ethene,<sup>58</sup> and a number of mono- and 1,1-disubstituted ethenes<sup>58,129</sup> in moderate to good yields. Some of the products showed useful insecticidal activity.<sup>127-130</sup> The products were originally formulated as having a bridge-head nitrogen atom, e.g., **131** (Scheme 48), addition being stereospecific and giving the endo-isomers. However, X-ray crystallographic measurements on two adducts show their (endo) structures to be **132a**<sup>131</sup> and **132b**,<sup>132</sup> indicating a [1,5]-chlorine shift to give the 3*H*-pyrrole **133** before cyclization. The product **132c** has been prepared (83%), although attempts to prepare adducts from other dienophiles failed,<sup>133</sup> since the cycloaddition is apparently slow as compared with side reactions. Simple calculation shows that, in terms of enthalpy changes, formation of the adduct from the 3*H*-pyrrole **133** is more favorable than that from **21**.<sup>133</sup>



SCHEME 48

<sup>128</sup> J. L. Wong, German Patent 2,511,713 [CA 84, 31035 (1976)].

<sup>129</sup> J. L. Wong, U.S. Patent 4,087,434 [CA 89, 129392 (1978)].

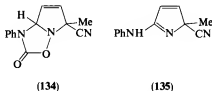
<sup>130</sup> J. L. Wong, U.S. Patent 4,081,488 [CA 90, 54844 (1979)].

<sup>131</sup> P. Marsh and D. E. Williams, *Acta Crystallogr., Sect. B* **B35**, 2241 (1979).

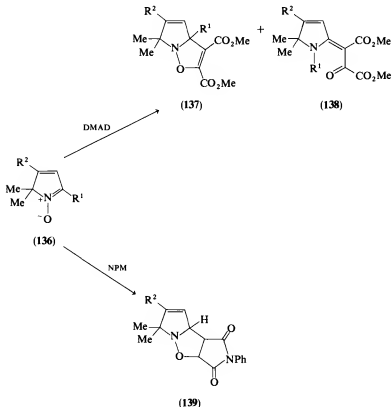
<sup>132</sup> P. H. Daniels, J. L. Wong, J. L. Atwood, L. G. Canada, and R. D. Rogers, *J. Org. Chem.* **45**, 435 (1980).

<sup>133</sup> M. E. Jung and J. J. Shapiro, *J. Am. Chem. Soc.* **102**, 7862 (1980).

b. *1,3-Dipolar Cycloadditions.* 2*H*-Pyrrole *N*-oxides are nitrones, and as such undergo 1,3-dipolar cycloaddition with suitable dipolarophiles. Thus, compound **121a** ( $R = H$ )<sup>117a</sup> reacts with phenyl isocyanate in boiling toluene to give a mixture of two products (**134** and **135**) in low yields; the



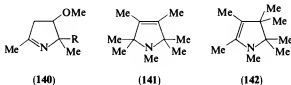
former is not converted to the latter in boiling chlorobenzene.<sup>117</sup> Likewise, the *N*-oxides **136** with DMAD give two products (**137** and **138**, Scheme 49); **138** arises from rearrangement of **137** and is the only product for  $R^1 = H$ .



SCHEME 49

*N*-Phenylmaleimide (NPM) also forms adducts (**139**; single isomer, quantitative yield), but only when  $R^1 = H$ .<sup>107</sup>

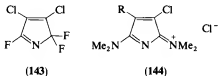
c. *Other Additions*. Methanol adds photochemically (254 nm) to 2,2,5-trialkyl-2*H*-pyrroles (although not under acid or base catalysis) to give the pyrrolines **140** ( $R = n\text{-Pr}$  or allyl) in high yields.<sup>134</sup> Methylmagnesium iodide can add to the salts of 2*H*-pyrroles both by 1,2-addition and by conjugate addition.<sup>17</sup> The methiodide of compound **1**, for example, gives a mixture of products (**141** and **142**) the latter predominating. Compound **1** also forms a tricarbonyl-iron complex<sup>135</sup> analogous to complexes formed from 2*H*-imidazoles<sup>135</sup> and from 4*H*-pyrazoles.<sup>136</sup>



## B. TRANSFORMATIONS OF SUBSTITUENTS

### 1. Polychloro-2*H*-Pyrroles

Pentachloro-2*H*-pyrrole (**21**) was converted to the trifluoro derivative **143** by excess silver(I) fluoride at  $135^\circ\text{C}$ <sup>57</sup> and to the salts **144** with *N,N*-dimethyl(trimethyl)silylamine ( $R = \text{Cl}$  or  $\text{NMe}_2$ , depending on the amount



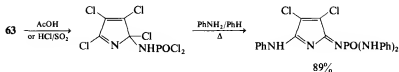
of silylamine used) at low temperatures.<sup>59</sup> The trichlorophosphinimine derivatives **63** and **64** have been transformed to a variety of products by acetic acid, methanol, and amines, an example being shown in Scheme 50.<sup>60,61</sup>

<sup>134</sup> J. M. Patterson, R. L. Beine, and M. R. Boyd, *Tetrahedron Lett.*, 3923 (1971).

<sup>135</sup> H. Tom Dieck and H. Bock, *J. C. S. Chem. Commun.*, 678 (1968).

<sup>136</sup> H. Tom Dieck, I. W. Renk, and H. P. Brehn, *Z. Anorg. Allg. Chem.* **379**, 169 (1970) [*CA* **74**, 27599 (1971)].



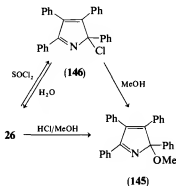


SCHEME 50

## 2. 2H-Pyrroles with 2-Oxygen-Linked Substituents

Several reactions appear to proceed via ring-opened intermediates.

a. *2-Hydroxy Group*. The tetraphenyl compound **26** has been converted to the 2-methoxy derivative **145** (Scheme 51), either by treatment with methanolic hydrogen chloride<sup>42</sup> or via the chloro compound **146**.<sup>44</sup> Similarly, the *N*-oxide **87** gave its 2-methoxy analog (**150**), both with methanolic hydrogen chloride<sup>74</sup> and by treatment with strong base followed by methyl iodide.<sup>75</sup>



SCHEME 51

b. *2-Hydroperoxy Group*. On treatment with hydrochloric acid, the hydroperoxide **40** gave the hydrochloride salt of **26** together with hydrogen peroxide and a blue-green fluorescence.<sup>44</sup> The compounds **40**,<sup>44,47,48</sup> **43**,<sup>50</sup> and **45**<sup>51</sup> were all reduced to the corresponding 2-hydroxy derivatives by potassium iodide in acetic acid, but the less substituted analogs **41**<sup>48</sup> and **42**<sup>50</sup> are acid sensitive and gave other products. However, **41** was reduced successfully by triphenylphosphine.<sup>48</sup>

c. *Others*. The 2-methoxy analog of **87** is hydrolyzed with water to **87**<sup>74</sup>; the benzoate **34** is converted to **26** with methanolic sodium hydroxide.<sup>46</sup>

3. *Eliminations*

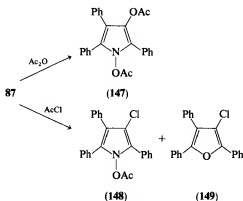
Base-induced loss of hydrogen iodide from methiods of 2*H*-pyrroles have been reported by several workers,<sup>11,12,16,17,119</sup> giving methylene pyrrolines **3** and **7** and analogs with different substituents.

## C. REMOVAL OF SUBSTITUENTS

All examples reported have involved the loss of a 2-substituent from a 2*H*-pyrrole, accompanied by rearomatization to a 1*H*-pyrrole.

1. *Loss of 2-Oxy Substituent*

a. *2-Hydroxy Group*. Compound **26** is reduced to tetraphenylpyrrole (**23**) by hydrogen iodide, sodium hydrogen sulfite, zinc and acetic acid, sodium borohydride, or phosphorus trichloride<sup>42</sup>; the *N*-oxide of **26** is converted to the *N*-hydroxypyrrole (**44**) by hydroxylamine hydrochloride.<sup>51</sup> The *N*-oxide **87**, on heating with acetic anhydride or acetyl chloride, gave the products **147** and **148** respectively, the latter together with the furan **149** (Scheme 52).<sup>75</sup> A mechanism was suggested which involved a [1,3]-acetoxy shift.

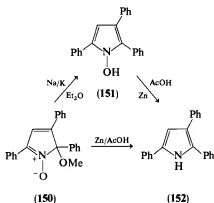


SCHEME 52

b. *2-Hydroperoxy Group*. Conversion to parent 1*H*-pyrroles takes place with hydroperoxides **40** and **41** simply by heating (80°–110°C)<sup>44,47,48</sup>;

zinc and acetic acid bring about an analogous transformation of the hydroperoxides **42** and **43**.<sup>50</sup> The *N*-oxide **45** is reduced to **44** (Scheme 13) by hydroxylamine hydrochloride.<sup>51</sup>

c. *Others*. The methoxy *N*-oxide **150** with sodium/potassium alloy is reduced to the *N*-hydroxypyrrole **151** and further to triphenylpyrrole (**152**) with zinc and acetic acid (Scheme 53).<sup>74</sup>



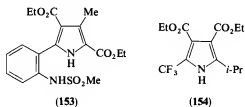
SCHEME 53

## 2. Loss of 2-Ester Group

Known examples of this transformation have been referred to in Sections II,A,3 (Scheme 6)<sup>30</sup> and II,B,1,b (Scheme 22).<sup>66-69</sup>

## 3. Others

Pentachloro-2*H*-pyrrole (**21**) is reduced by sodium amalgam and acetic acid to 2,3,4,5-tetrachloropyrrole.<sup>36</sup> The spiro compound **55** is hydrolyzed to **153** (69%) by concentrated hydrochloric acid,<sup>56</sup> and the adduct **105** is cleaved by base to the 1*H*-pyrrole **154**.<sup>88</sup>



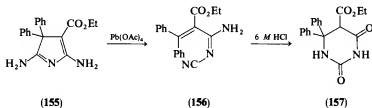
## D. RING CLEAVAGE REACTIONS

## 1. 2-Hydroxy and 2-Hydroperoxy Compounds

The ring-opening reaction of **26** to give *cis*-dibenzoylstilbene (**27**) via the imine **25** has already been discussed (Section II,A,5,a),<sup>41,42</sup> as has the interconversion of structures **87** and **88** (Scheme 26, Section II,B,2,a) with change in pH.<sup>74,75</sup> Thermolysis of the hydroperoxide **40** in boiling methanol gave a mixture of products (**29–31**), together with a small amount of tetraphenylpyrrole (**23**) by deoxygenation.<sup>44</sup> The mechanism of this chemiluminescent reaction is discussed in Section IV,E,5. A compound analogous to **29** was formed from the hydroperoxide **42** on treatment with potassium iodide in acetic acid.<sup>50</sup>

## 2. Cleavage of Other Isopyrrole Rings

The use of ozonolysis to establish the structure of pentamethyl-2*H*-pyrrole (**1**) was described earlier (Section II,A,2).<sup>16</sup> Treatment of pentachloro-2*H*-pyrrole with silver(I) fluoride gave in addition to the fluoride (**143**), the bis(acid fluoride) of dichloromaleic acid.<sup>57</sup> Oxidation of the diamino ester **155** with lead tetraacetate led to the cyanoimine **156**, which in turn was cyclized to the pyrimidine **157** (Scheme 54).<sup>137</sup>



SCHEME 54

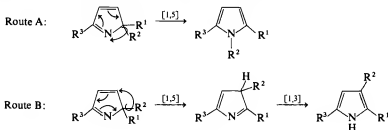
## E. REARRANGEMENTS

1. 2*H*-Pyrroles to 1*H*-Pyrroles

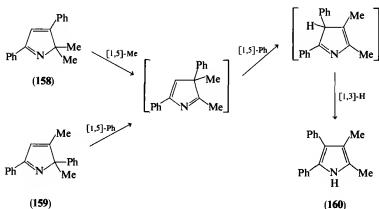
Rearrangement of 2*H*-pyrroles to the thermodynamically more stable 1*H*-isomers can be envisaged as occurring via a thermally allowed suprafacial [1,5]-sigmatropic shift by a C-2 substituent, either to nitrogen (route A,

<sup>137</sup> A. Foucaud and M. Baudru, *C. R. Hebd. Seances Acad. Sci., Ser. C* **276**, 301 (1973).

Scheme 55) or to C-3 followed by a tautomeric [1,3]-proton shift (route B). Although rearrangements by route B have been observed in a number of cases,<sup>18,19,98,101,102</sup> only one by route A has been reported<sup>56</sup> and that in a situation in which all carbons were fully substituted. Intuitively, route A should be preferred since it does not involve the thermodynamically less stable *3H* intermediate. It seems that the aromaticity of the *N*-substituted pyrrole product (route A) must develop late in the rearrangement process, a suggestion that has been made to explain analogous behavior in *3H*-pyrazoles.<sup>138</sup> Rearrangements by route B have been carried out at temperatures between 140° and 550°C, both with and without solvent. Yields are generally high and, when the substituents *R*<sup>1</sup> and *R*<sup>2</sup> are different, selectivity is observed. Thus, an ester group migrates exclusively in preference to methyl<sup>98</sup> or nitrile,<sup>102</sup> and the 1-phenylethyl group (with 35% retention of optical activity) in preference to methyl.<sup>19</sup> In some cases, two products have



SCHEME 55

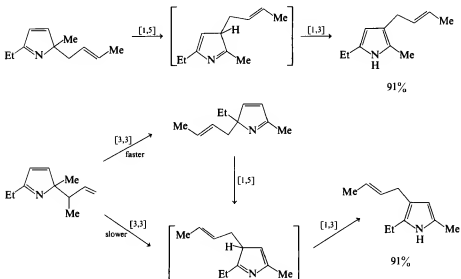


SCHEME 56

<sup>138</sup> W. J. Leigh and D. R. Arnold, *Can. J. Chem.*, **57**, 1186 (1979).

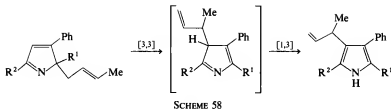
been isolated, selectivity being highest at low temperatures and decreasing as the temperature is raised.<sup>18,101</sup> When C-3 is substituted, two consecutive [1,5]-shifts to carbon sites occur, still apparently in preference to route A. Thus, the isomers **158** and **159** (in pyridine/benzene at 270°C) rearrange to the same product (**160**) (Scheme 56).<sup>115</sup>

The presence of a 2-allyl group introduces another complexity due to the possibility of [3,3]-sigmatropic shifts. By analyzing the <sup>1</sup>H NMR spectra of the pyrolysates of various substituted 2-allyl-2H-pyrroles at different time intervals, Patterson *et al.*<sup>139</sup> showed that *trans*- and *cis*-crotyl groups migrate predominantly by a [1,5]-shift from C-2 to C-3 without inversion (Scheme 57). However, the  $\alpha$ -methylallyl group migrates with inversion by two different routes involving competitive [3,3]-shifts, the larger rate of migration to C-5 being explained in terms of a lower-energy productlike (2H- rather than 3H-pyrrole) transition state.<sup>139</sup> The proposed<sup>140</sup> chairlike transition state was supported by the faster rate of migration of *trans*-crotyl as compared with that of *cis*-crotyl.<sup>139</sup> An apparently conflicting report of a [3,3]-sigmatropic shift by the allyl and *trans*-crotyl groups<sup>116</sup> (Scheme 58)



<sup>139</sup> J. M. Patterson, J. D. Ferry, J. W. de Haan, and M. R. Boyd, *J. Am. Chem. Soc.* **97**, 360 (1975).

<sup>140</sup> J. M. Patterson, J. W. de Haan, M. R. Boyd, and J. D. Ferry, *J. Am. Chem. Soc.* **94**, 2487 (1972).



can probably be accounted for by inhibition of a [1,5]-shift to C-3 due to the 3-phenyl substituent.

## 2. 3*H*-Pyrroles to 1*H*-Pyrroles.<sup>6,118</sup>

In the rearrangement of **122** (Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>) under acidic conditions, the anisyl group migrated from C-3 to C-4 to give a 1*H*-pyrrole, but under basic conditions it was the phenyl group that migrated, giving an isomeric 1*H*-pyrrole. An ionic mechanism consistent with these results was suggested.

## 3. 3*H*-Pyrroles to 2*H*-Pyrroles

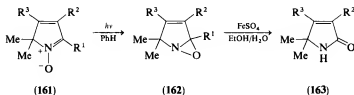
The 3*H*-pyrrole **2** isomerizes thermally to **1**, the reaction rate being enhanced by hydrogen-bonding solvents and strongly catalyzed by acid. The rearrangement appears to be of the Wagner–Meerwein type rather than sigmatropic. It is irreversible, and ethyl was shown to migrate in preference to methyl.<sup>7</sup> In contrast, the rearrangement of **21** to its 3*H*-isomer appears to be reversible.<sup>132,133</sup>

## 4. Others with Ring Remaining Intact

a. *2-Hydroxy-2H-pyrroles*. Compound **26** rearranges in high yield to the pyrrolinone **28** thermally and by acid or base catalysis.<sup>42–44,47,48</sup> Analogous compounds undergo a similar isomerization.<sup>50,54,55</sup> The mechanism is probably ionic.<sup>48</sup>

b. *N-Oxides*. Irradiation of the *N*-oxides **161** in benzene at 300 nm gives high yields of the oxazirines **162**, which can be reduced to pyrrolinones **163** in good yields (Scheme 59).<sup>141</sup> Rearrangements of **87** are shown in Scheme 52.<sup>75</sup>

<sup>141</sup> D. St. C. Black and N. A. Blackman, *Aust. J. Chem.* **32**, 2035 (1979); D. St. C. Black, N. A. Blackman, and L. M. Johnstone, *ibid.*, 2041.

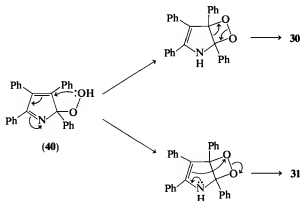


SCHEME 59

c. *Others.* Treatment of the 3*H*-pyrrole **36** with acid gives the 2,3-epoxide.<sup>40</sup>

### 5. Rearrangements with Ring Fission

Thermolysis of **40** in methanol gives a mixture of products, including **29**, **30**, and **31** (and some **23** from deoxygenation).<sup>44,48</sup> Products **30** and **31** appear to arise via different (chemiluminescent) pathways (Scheme 60),<sup>48</sup> although **29** is probably derived from **31** by hydrolysis.



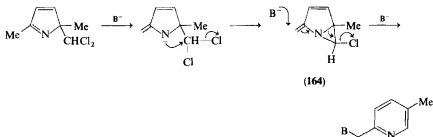
SCHEME 60

### 6. Rearrangements to Other Heterocycles

a. *Pyrrole-Dichlorocarbene Adducts.* The coproduction of 2-dichloromethyl-2*H*-pyrroles and 3-chloropyridines in the reaction between dichlorocarbene and pyrroles (Scheme 5) and evidence that the two products have a common intermediate (Scheme 7) were discussed in Section II,A,3. Jones and Rees<sup>31</sup> reported that the adduct **13** ( $R^1 = R^3 = \text{Me}$ ;  $R^2 = \text{H}$ ) gave

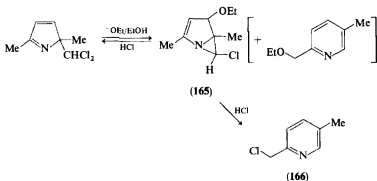


2,5-dimethylpyridine with sodium hydride, and 2-ethoxymethyl-5-methylpyridine with sodium ethoxide, and postulated an aziridine intermediate (**164**) (Scheme 61).

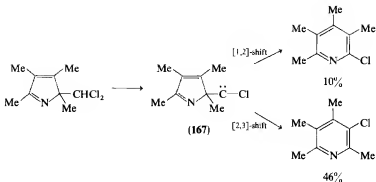


SCHEME 61

Coproduction of 2-ethoxymethyl- and 4-ethoxymethyltrimethylpyridines from **13** ( $R^1 = R^2 = R^3 = \text{Me}$ ) was accounted for in terms of two isomeric aziridines.<sup>31</sup> Nicoletti and Forcellese<sup>32</sup> isolated the intermediate **165** from the reaction with sodium ethoxide (Scheme 62) and suggested that this might be the true intermediate in the formation of pyridines, since it could be converted to **166** (and starting material) with hydrochloric acid. However, later work suggested that the ring enlargement might not necessarily occur via **165** or analogous structures.<sup>29</sup> It has also been reported that dichlorocarbene adducts are converted to chloropyridines by very strong base (butyllithium), the chlorocarbene **167** being a likely intermediate (Scheme 63).<sup>33</sup>

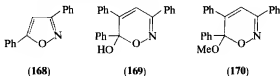


SCHEME 62



SCHEME 63

b. *Others.* Pyrolysis of the *N*-oxide **87** gives benzaldehyde and the isoxazole **168**, presumably via **169**, since the methoxy analog **150** gives only **170**.<sup>142</sup> This rearrangement brings to mind the conversion of the oxazine **121b** to the 2*H*-pyrrole *N*-oxide **121a**.<sup>117a</sup>



## V. Appendix: Additional Papers

A few additional references have been found since this review was written. They are cross referenced here by relevant Sections.

Section II,A,5,a: Oxidation of 2,5-diphenylpyrrole with potassium dichromate in aqueous acetic acid gives a mixture of five products, four of which contain 2*H*-pyrrole rings.<sup>143</sup> This work is contrasted with that describing the oxidation of 2,3,5-triphenylpyrrole under similar conditions.<sup>40</sup>

Section II,B,1,a: The bromotrinitrile shown in Scheme 21 with  $\text{R}^1 = \text{R}^2 = \text{PhCH}_2$ , reacts with phthalimidyliminotriphenylphosphorane to give a 3*H*-pyrrole related to structures **67** and **68**.<sup>144</sup>

<sup>142</sup> A. H. Blatt, *J. Org. Chem.* **15**, 869 (1950).

<sup>143</sup> S. Petruso, L. Lamartina, O. Migliara, and V. Sprio, *J. C. S. Perkin I*, 2642 (1981).

<sup>144</sup> P. Merot, C. Gadreau, and A. Foucaud, *Tetrahedron* **37**, 2595 (1981).

Section II,C,3,a: In the presence of  $\text{Mo}(\text{CO})_6$ , 2,2-dimethyl-3-phenyl-2*H*-azirine reacts with alkynoic esters via an unusual cleavage of the  $\text{C}=\text{N}$  bond to give 2*H*-pyrroles in low yield.<sup>145</sup>

Sections II,E,5: Thermolysis of certain 5-pyrrolidino-1-vinyl-4,5-dihydro-1,2,3-triazoles gives a mixture of an *N*-vinylamidine and a 2*H*-pyrrole. The yield of the latter increases with decreasing solvent polarity, suggesting a radical mechanism for its formation.<sup>146</sup>

Section III,B,3: The chemical shift of the ring proton at C-5 in 2*H*-pyrroles unsubstituted at this position has been reported in  $\text{CDCl}_3$  at  $\delta$  8.15<sup>145</sup> and at  $\delta$  8.55.<sup>146</sup>

Section III,B,4: The  $^{13}\text{C}$ -NMR signals for C-3 and C-5 in a 2*H*-pyrrole unsubstituted at both positions have been assigned in  $\text{CDCl}_3$ , respectively, at  $\delta$  153.6 and  $\delta$  161.3.<sup>146</sup>

Section IV,A,2,a: Pentachloro-2*H*-pyrrole (**21**) behaves as a diene via the rearranged 3*H*-pyrrole form **133** in its reaction with *trans*-1,3-pentadiene, giving a product **132** having  $\text{R} = \text{trans-1-propenyl}$ . However, the mode of cycloaddition is reversed with cyclopentadiene, the 2*H*-pyrrole (**21**) reacting directly as a dienophile at the 3-4  $\text{C}=\text{C}$  bond. With 1,3-cyclohexadiene, both modes of cycloaddition occur simultaneously. Steric factors rather than relative HOMO and LUMO energies are thought to determine the reaction course.<sup>147</sup>

<sup>145</sup> A. Inada, H. Heimgartner, and H. Schmid, *Tetrahedron Lett.*, 2983 (1979).

<sup>146</sup> Y. Nomura, Y. Takeuchi, S. Tomada, and M. M. Ito, *Bull. Chem. Soc. Jpn.* **54**, 2779 (1981).

<sup>147</sup> B. K. Rammash, C. M. Gladstone, and J. L. Wong, *J. Org. Chem.*, **46**, 3036 (1981).

## 1,2,4-Thiadiazoles

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## I. Introduction

The 15-year period since 1965, the date of a previous review of the chemistry of 1,2,4-thiadiazoles, has witnessed impressive developments in all branches of heterocyclic chemistry, and 1,2,4-thiadiazoles have been no exception. Rapid progress has widened the existing knowledge and deepened the understanding of the nature and behavior of this ring system. Moreover, 1,2,4-thiadiazole derivatives have recently found important uses and have attained an industrial and economic importance which they did not possess 15 years ago.

The accumulation of this new knowledge (the published bulk of which amounts to three times the total of all that had gone before) appeared to justify the preparation of a supplement to the existing reviews. Of these, Bambas' survey of 1952<sup>1</sup> is still valuable, because of its detailed treatment of the earlier difficulties and controversies concerning structural questions.

<sup>1</sup> L. L. Bambas, "Five-Membered Heterocyclic Compounds," p. 35 et seq. Wiley (Interscience), New York, 1952.

Sherman's contribution,<sup>2</sup> focusing on the synthesis of this ring system (before 1956) formed a concise chapter in Elderfield's "Heterocyclic Compounds." The review<sup>3</sup> which appeared in 1965 in a previous volume of the present series, while emphasizing more recent developments, aimed at giving a comprehensive account of the subject from its beginnings. Since 1970 progress has been recorded biannually in the *Specialist Reports*<sup>4</sup> of the Chemical Society. Narrower aspects of the subject, including accounts of the 1,2,4-thiadiazole 1,1-dioxides ("cyclic  $\alpha$ -aminosulfonamides")<sup>5</sup> and of fluorinated 1,2,4-thiadiazoles<sup>6</sup> have been incidental features of more general reports. The present survey attempts to review the advances of the past 15 years so as to provide, in conjunction with the original chapter,<sup>3</sup> a complete account of the chemistry of 1,2,4-thiadiazoles.<sup>3a</sup>

The task of recent investigators has in some respects been lightened by the fact that the chemistry of 1,2,4-thiadiazoles has for some time been a well-charted area, containing many clear points of reference. Indeed, a large proportion of the new knowledge is concerned with variations and extensions of established reactions and syntheses, the soundness and usefulness of which have stood the test of time. Parallel with this work of consolidation, advances of striking novelty have been made, and have opened up new fields to research. Among these achievements, several ingenious new syntheses are noteworthy and are referred to in their proper place. A matter of special interest has been the growing awareness of the role of structures of the heteropentalene type,<sup>7,8</sup> and of the "bond switches" associated with them, in many reactions of 1,2,4-thiadiazole derivatives. The recognition of their significance over the past decade has chiefly been the result of X-ray crystallographic techniques.

Since the 1,2,4-thiadiazole ring system does not occur in natural products, and since no important uses for compounds of this class had been found by

<sup>2</sup> W. A. Sherman, *Heterocycl. Compd.* **7**, 558 (1961) (covering the literature to 1956).

<sup>3</sup> F. Kurzer, *Adv. Heterocycl. Chem.* **5**, 119 (1965).

<sup>3a</sup> The substance of this chapter is based on publications reported in *Chemical Abstracts* (up to Volume 92, incl.), but some later papers are also noticed. Completeness of coverage has been aimed at, but technical or biological reports are often gathered into a single multiple reference.

<sup>4</sup> F. Kurzer, *Org. Compd. Sulphur, Selenium Tellurium* **1**, 446 (1970); **2**, 721 (1973); **3**, 679 (1975); **4**, 422 (1977); M. Davis, *ibid.* **5**, 435 (1979); continued in G. V. Boyd, P. A. Lowe, and S. Gronowitz, *Heterocycl. Chem.* **1**, 155 (1980).

<sup>5</sup> A. Lawson and R. B. Tinkler, *Chem. Rev.* **70**, 593 (1970).

<sup>6</sup> B. Bouchet, C. Coquelet, and J. Elguero, *Bull. Soc. Chim. Fr.*, 171 (1977).

<sup>7</sup> E. Klingsberg, *Q. Rev., Chem. Soc.* **23**, 537 (1969); N. Lozac'h, *Adv. Heterocycl. Chem.* **13**, 161 (1971).

<sup>8</sup> D. Leaver, *Org. Compd. Sulphur, Selenium Tellurium* **5**, 310 (1979); R. J. S. Beer, *ibid.* **4**, 300 (1977), and preceding volumes.

1965 (even though some were foreshadowed), their study had long remained a matter of academic interest only. This is no longer true. 1,2,4-Thiadiazoles have gained a position of technical and commercial importance by the introduction of Terrazole as an effective agricultural fungicide, of organophosphorus esters as pesticides, by the production of monazo dyes especially suitable for dyeing polymers, and by their use as intermediates in other processes. This has not only generated an extensive patent literature dealing with the immediate practical applications, but has undoubtedly intensified interest in 1,2,4-thiadiazoles in general, and given a renewed impetus to all forms of fundamental research into this ring system.

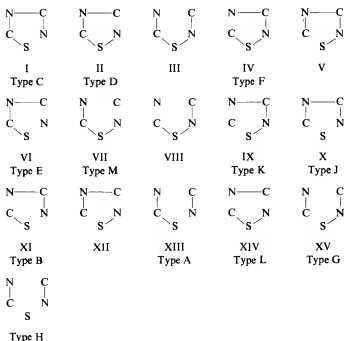
In the interest of continuity, the general plan of the present review adheres, as far as possible to that previously adopted.<sup>3</sup> Contractions and deviations are sign-posted by cross-references. A division between the hetero-aromatic parent compounds and their reduced forms (thiadiazolines, thiadiazolidines) has not been made because it would lead to a great deal of repetition. A given synthesis, for example, may often yield the heteroring at each level of reduction, depending on the degree of substitution of the starting materials. Differences in properties of the three series are emphasized where appropriate. As before,<sup>3</sup> condensed polycyclic ring systems incorporating 1,2,4-thiadiazole are outside the scope of this review, but the extension of several general thiadiazole syntheses to the production of such fused structures are fully covered.

## II. Synthesis of 1,2,4-Thiadiazoles

A wide range of 1,2,4-thiadiazoles has long been accessible by well-established syntheses.<sup>3</sup> Their soundness and usefulness have been confirmed by their continued and successful use, and their scope has been extended. The versatile syntheses originally introduced by Goerdeler have been a particularly fruitful source of new 1,2,4-thiadiazoles, and are now the basis of several large-scale processes. The conversion of thioureas to 1,2,4-thiadiazoles has been reinvestigated repeatedly, and some of its remaining unexplained features have been clarified. Novel synthetic methods have also been developed. Among these a group of reactions involving the cycloaddition of nascent thiaziridines and heterocumulenes provides a general synthesis, the interpretation of which presents particularly interesting aspects. Chlorothioformyl chloride, now readily available, furnishes the starting point of another new route that has been exploited rapidly in various directions. Several of the syntheses are suitable for constructing condensed ring systems incorporating the 1,2,4-thiadiazole nucleus.

In accordance with established practice,<sup>3</sup> the syntheses of 1,2,4-thiadiazoles are classified according to the nature of the fragments, from which the heterocyclic ring is built. The number of possible ways in which this can be done is in fact not large: there are five ways, in each case, (i) of ring closing a preformed chain consisting of the five appropriate atoms in the correct sequence (see Scheme 1, I–V), (ii) of condensing a chain of four atoms with the complementary fifth atom (VI–X), and (iii) of performing  $[2 + 3]$  cyclo-additions (XI–XV). The number of permutations does increase when three or more smaller fragments join to form the ring: since this requires the operation of reactions of the third or higher order, these are not considered in detail. One such reaction is, nevertheless, on record (Type H).

Since almost all the syntheses previously reported fitted into one of only three categories, the full system (Scheme 1) was originally not adopted, the existing divisions being denoted as types A–C. Subsequently, the classification was continued in a chronological rather than systematic order, new categories being lettered consecutively as they arose.<sup>4</sup> Although the resulting system is not as methodical as one might wish, it would hardly be helpful,



SCHEME 1



at this stage, to renumber these categories, the more so because almost all the important new syntheses have again proved to belong to types A-C. Nevertheless, at least 10 of the possible 15 routes (I-XV) have by now been translated into practical reality in the laboratory. In classifying the individual syntheses, the decisive guidelines are the structures of the actual starting material contributing the atoms to the final heteroring. This point of view disregards the mechanism of the reactions, but results in assignments that are less likely to require later modification.

## A. TYPE A SYNTHESSES



### 1. Oxidation of Thioamides

Hofmann's classical synthesis of 3,5-disubstituted 1,2,4-thiadiazoles by the oxidation of thioamides (1869)<sup>3</sup> continues to be further exemplified. The oxidants employed include iodine,<sup>9-11</sup> bromine,<sup>12</sup> chlorine,<sup>13</sup> and nitrous acid,<sup>14</sup> as well as *N*-chlorobenzamidine (which is recovered as benzamidine)<sup>15</sup> and *N*-sulfinyl-*p*-toluenesulfonamide (which evolves sulfur dioxide in the process).<sup>16</sup> Irradiation with UV light in the presence of oxygen effects the same reaction, but has not been used on a preparative scale.<sup>17</sup>

1,2,4-Thiadiazoles may in fact become unwanted by-products in other syntheses when thioamides are used<sup>18,19</sup> or formed *in situ* in an oxidative environment.<sup>20</sup> The cause of the decomposition of the drug Ethionamide (2-ethyl-4-thioamidopyridine), when stored in pharmaceutical preparations,

<sup>9</sup> W. R. Sherman and A. von Esch, *J. Med. Chem.* **8**, 25 (1965).

<sup>10</sup> B. Kurgane and S. Hillers, *Khim. Geterotsikl. Soedin.*, 323 (1966) [*CA* **66**, 28,597m (1967)].

<sup>11</sup> P. H. Deshpande, *J. Indian Chem. Soc.* **46**, 1096 (1969).

<sup>12</sup> C. Runti and A. Stener, *Ann. Chim. (Rome)* **53**, 1370 (1963).

<sup>13</sup> J. V. Burakevich, A. M. Lore, and G. P. Volpp, *Chem. Ind. (London)*, 238 (1970).

<sup>14</sup> M. Bahadir, S. Nitz, H. Parlar, and F. Korte, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **34B**, 768 (1979).

<sup>15</sup> E. Haruki, T. Inaike, and E. Imoto, *Bull. Chem. Soc. Jpn.* **41**, 1361 (1968).

<sup>16</sup> G. Kresze and A. Maschke, German Patent 1,167,846 (1964); [*CA* **61**, 3118 (1964)].

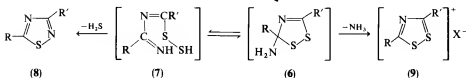
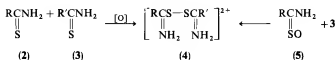
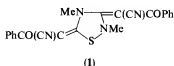
<sup>17</sup> M. Bahadir, S. Nitz, H. Parlar, and F. Korte, *J. Agric. Food Chem.* **27**, 815 (1979).

<sup>18</sup> K. T. Potts and J. L. Marshall, *J. Org. Chem.* **41**, 129 (1976).

<sup>19</sup> G. Barnikow, V. Kath, and H. Conrad, *J. Prakt. Chem.* **31**, 262 (1966).

<sup>20</sup> G. M. Filho, J. O. Falcao de Moraes, J. G. da Costa, and F. S. de Azevedo, *An. Acad. Bras. Cienc.* **35**, 197 (1963) [*CA* **60**, 5481 (1964)].

has been traced to this oxidation.<sup>21</sup> A more unusual example of the reaction is the oxidation of  $\alpha$ -benzoyl- $\alpha$ -cyano-*N*-methylthioacetamide [PhCOCH(CN)CSNHMe] by iodine in chloroform-triethylamine to the 1,2,4-thiadiazolidine (1), the structure of which was assigned on the basis of spectral data.<sup>22</sup>



Significantly, treatment of arylthioamides (2) with oxidants (hydrogen peroxide, iodine) in formic or glacial acetic acid, preferably in the presence of perchloric acid, produces good yields of 3,5-disubstituted 1,2,4-dithiazolium salts (9) rather than 1,2,4-thiadiazoles (8). The interaction of arylthioamides (3) and thiobenzamide *S*-oxide (5) (the isolable primary oxidation product of thiobenzamide<sup>3</sup>) proceeds analogously in acid media and provides access to examples of 9 incorporating nonidentical 3- and 5-substituents. The action of ammonium acetate in glacial acetic acid converts the 1,2,4-dithiazolium salts (9) smoothly and rapidly into the corresponding 1,2,4-thiadiazoles (8), with evolution of hydrogen sulfide. On the basis of these observations, the following unifying mechanism for the oxidations has been suggested: disulfides [dithiobis(benzylimines)] (4) are first formed and are cyclized to 1,2,4-dithiazolidines (6); in strongly acid media protonation of the amino group and elimination of ammonia results in the dithiazolium salts (9). In weakly acidic or neutral media, however, ring scission to amidines (7), followed by loss of hydrogen sulfide, yields the thiadiazoles (8)<sup>23</sup> (see also Ref. 24).

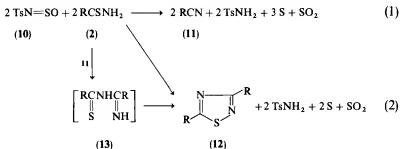
<sup>21</sup> T. Cieszynski, *Acta Pol. Pharm.* **31**, 651 (1974).

<sup>22</sup> H. Kunzek, E. Nesener, and J. Voigt, *Z. Chem.* **18**, 172 (1978).

<sup>23</sup> J. Liebscher and H. Hartmann, *Justus Liebigs Ann. Chem.*, 1005 (1977).

<sup>24</sup> I. Shibuya, *Nippon Kagaku Kaishi*, 389 (1979) [*CA* **90**, 186,869 (1979)].

*N*-Sulfinylsulfonamides (**10**, Ts = *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>) are known to function as highly reactive sulfinylating agents, converting alcohols and hydrazides to their respective sulfinyl derivatives [e.g., (RO)<sub>2</sub>SO, RCONHN=SO]. With thioamides the reagent yields nitriles (Eq. 1), or 3,5-disubstituted 1,2,4-thiadiazoles (Eq. 2). The production of the latter (**12**) is favored by a choice of suitable conditions, but is usually attended by nitrile formation, which may become the dominant reaction.<sup>25</sup> *N,N*-Diphenylthiourea similarly yields diphenylcyanamide (**11**, R = Ph<sub>2</sub>N, 60%) and 3,5-bis-(diphenylamino)-1,2,4-thiadiazole (**12**, R = Ph<sub>2</sub>N, 8%), while *O*-ethylthiocarbamate (**2**, R = EtO) is converted to 3,5-diethoxy-1,2,4-thiadiazole (**12**, R = EtO, 25%).<sup>25</sup>



*N*-Thiobenzoylbenzamidide (**13**) is isolable in high yield in the early stages of experiments starting with thiobenzamide. The production of the 1,2,4-thiadiazole (**12**, R = Ph) occurs undoubtedly by oxidative cyclization of this linear intermediate; various aspects of the possible mechanism have been discussed.<sup>25</sup>

An interesting formation of the thiadiazole (**12**, R = pyrid-4-yl) occurs when 4-methylpyridine containing dissolved sulfur is heated with ammonia under pressure. The same reaction converts 2-methylpyridine to the 2-thioamide or 2-nitrile, depending on the conditions. Thiadiazole formation may thus occur by the usual condensation of these two components to the thioacylamidine (**13**, R = pyrid-4-yl), which is cyclized by the oxidizing action of the sulfur.<sup>26</sup>

## 2. Oxidation of Thioureas

Depending on the conditions, the oxidation of substituted thioureas may give rise to one or more possible products. The diversity of the course of

<sup>25</sup> G. Kresze, A. Horn, R. Philippson, and A. Trede, *Chem. Ber.* **98**, 3401 (1965).

<sup>26</sup> R. Mayer, H. D. Eilhauer, and R. Keck, German (East) Patent 54,362 (1967) [*CA* **67**, 100,016m (1967)].

this reaction, and the variety of its products have been a challenge to successive groups of investigators. Significant progress has recently been made, especially by the use of spectral and X-ray diffraction techniques, but a full unifying interpretation of all the observations is not yet in sight. Compounds related to 3,5-diamino-1,2,4-thiadiazole are a prominent group among the oxidation products. The formal analogy of thioamides and thioureas thus extends to the production, on oxidation, of the 1,2,4-thiadiazole ring system from both (see Section, II.A.1).

a. *Arylthioureas*. The oxidation products of monoarylthioureas in protic media are the so-called "Hector's bases" (named after their discoverer, 1889), for which several possible structures have been discussed.<sup>1,3</sup> On the basis of the available chemical evidence, they were formulated<sup>27,28</sup> in 1961–1963 as **14a**, with the explicitly stated<sup>28</sup> reservation, that tautomeric forms were not excluded. A recent X-ray analysis<sup>29</sup> of the prototype of Hector's base (**14**, Ar = Ph)<sup>29a</sup> has confirmed this structure, and has shown that the compound assumes the 3-arylamino- $\Delta^2$ -1,2,4-thiadiazoline form (**14b**) in the solid state. Similarly the nonbasic keto compound ("Dost's keto compound")<sup>1,3</sup> obtained from Hector's base (**14b**) by the action of hydrochloric acid is also the 3-phenylamino tautomer (**15b**).<sup>30</sup> These forms (**14b**, **15b**) persist in dimethyl sulfoxide solution, as shown by <sup>15</sup>N- and <sup>13</sup>C-NMR measurements.<sup>31</sup>



In the course of the synthetic and structural studies, the list of Hector's bases derived from monoarylthioureas has lengthened.<sup>32–34</sup> The homolog

<sup>27</sup> C. P. Joshua, V. K. Verma, and K. S. Suresh, *Tetrahedron Lett.*, 663 (1961).

<sup>28</sup> F. Kurzer and P. M. Sanderson, *J. Chem. Soc.*, 3333 (1963); *Chem. Ind. (London)*, 1681 (1962).

<sup>29</sup> A. R. Butler, C. Glidewell, and D. C. Liles, *J. C. S. Chem. Commun.*, 652 (1978); *Acta Crystallogr., Sect. B* **34B**, 3241 (1978).

<sup>29a</sup> In the sequel, the term "Hector's base" without further qualification refers to the phenyl homolog (**14b**, R = Ph). Hector's bases are henceforth represented as **14b**, even when they appear as the tautomers (**14a**) in the relevant original papers.

<sup>30</sup> A. F. Cuthbertson, C. Glidewell, H. D. Holden, and D. C. Liles, *J. Chem. Res., Synop.*, 316 (1979).

<sup>31</sup> A. R. Butler, C. Glidewell, I. Hussein, and P. R. Maw, *J. Chem. Res., Synop.*, 114 (1980).

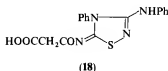
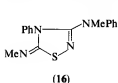
<sup>32</sup> C. P. Joshua, *Indian J. Chem.*, **1**, 391 (1963).

<sup>33</sup> K. Akiba, T. Tsuchiya, N. Inamoto, K. Onuma, N. Nagashima, and A. Nakamura, *Chem. Lett.*, 723 (1976).

<sup>34</sup> G. Barnikow and J. Boedeker, *Chem. Ber.*, **100**, 1394 (1967).

(14b, R = CH<sub>2</sub>Ph) obtained from benzylthiourea is noteworthy as an example of the aralkyl series; it yields derivatives with carbon disulfide, phenyl isothiocyanate, and acetic anhydride as expected,<sup>3</sup> and is reducible to the corresponding amidinothiourea by ring scission at the S—N bond.<sup>35</sup> The numerous procedures for performing the reaction<sup>1,3</sup> have continued to prove their general applicability, and have been added to by the inclusion of *N*-sulfinyl-*p*-toluenesulfonamide<sup>25</sup> and bis(arylsulfonylimino) sulfides [(ArSO<sub>2</sub>N=)<sub>2</sub>S]<sup>36</sup> as effective reagents. The former desulfurizes the phenylthiourea to phenylcyanamide in a parallel reaction, so that Hector's base (14b) and its adduct with phenylcyanamide are isolated side by side.<sup>25</sup> (See also Section c below, oxidative action of dithioformamides).

Hector's base is a strong monoacidic base (pK 13.5, from spectral data). According to <sup>13</sup>C-NMR measurements in trifluoroacetic acid, it is protonated predominantly at its exocyclic 2-imino group.<sup>37</sup> Its alkylation with sodium hydride-methyl iodide in dimethylformamide yields the 3,5-dimethyl derivative (16).<sup>31</sup> With Meldrum's acid (17), it reacts with elimination of acetone to yield a carboxylic acid formulated as 18, which is decarboxylated pyrolytically to the acetyl derivative of Hector's base.<sup>37</sup>



b. *Adduct Formation.* It has long been known<sup>1,3</sup> that Hector's bases form 1:1-adducts with carbon disulfide, isothiocyanate esters, cyanamides, as well as some other reagents, but their constitution has only been accurately established recently.

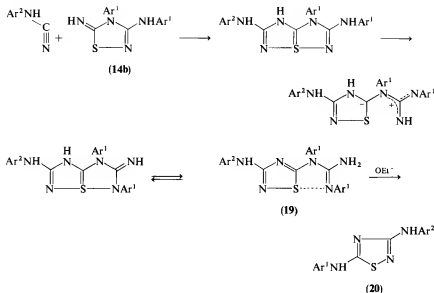
The structure of the adducts with arylcyanamides has been elucidated by an X-ray analysis of the tris-*p*-bromophenyl compound (19, Ar<sup>1</sup> = Ar<sup>2</sup> = *p*-C<sub>6</sub>H<sub>4</sub>Br). Adduct formation is therefore more complex than appears at first sight: it is visualized to proceed by initial 1,3-dipolar cycloaddition of the components, and is followed by the rearrangements shown (Scheme 2).<sup>33</sup> This supersedes a tentative different interpretation, proposed before the molecular dimensions (of 19) were known.<sup>38</sup> A number of such adducts (19, Ar<sup>1</sup>, Ar<sup>2</sup> = Ph or *p*-Tol) were readily obtained from the components in

<sup>35</sup> P. K. Srivastava and Y. R. Rao, *J. Indian Chem. Soc.* **40**, 803 (1963).

<sup>36</sup> E. S. Levchenko and B. N. Ugarov, *Zh. Org. Khim.* **4**, 1413 (1968).

<sup>37</sup> A. R. Butler, *J. Chem. Res., Synop.*, 50 (1978).

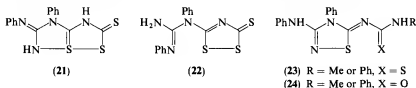
<sup>38</sup> K. Akiba, T. Tsuchiya, M. Ochiiumi, and N. Inamoto, *Tetrahedron Lett.*, 455 (1975).



SCHEME 2

tetrahydrofuran at  $70^\circ\text{C}$ . They were cleaved by ethanolic sodium ethoxide to 3,5-bis(arylamino)-1,2,4-thiadiazoles (20).<sup>38</sup> Their  $^{13}\text{C}$ -NMR spectra support the foregoing conclusion and suggest that their guanidino groups behave as electron donors, and their hetero rings as electron acceptors, attributable to N—S interaction.<sup>39</sup>

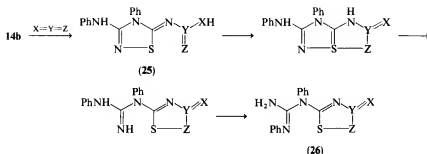
The adduct of Hector's base with carbon disulfide,<sup>1,3</sup> first regarded as 21,<sup>37</sup> has the solid state structure 22.<sup>40</sup> With isothiocyanate esters, simple 5-thioureido derivatives (23, 24) are obtained (see also Refs. 35, 41). The structure of the addition compound with methyl isothiocyanate, for example, is 23 ( $\text{R} = \text{Me}$ ) in both the crystalline and dissolved (DMSO) state, as determined by X-ray analysis, and  $^{15}\text{N}$ - and  $^{13}\text{C}$ -NMR measurements.<sup>31</sup>



<sup>39</sup> K. Akiba, T. Tsuchiya, N. Inamoto, K. Yamada, H. Tanaka, and H. Kawazura, *Tetrahedron Lett.*, 3819 (1976).

<sup>40</sup> A. R. Butler, C. Glidewell, and D. C. Liles, *Acta Crystallogr., Sect. B* **34B**, 2570 (1978).

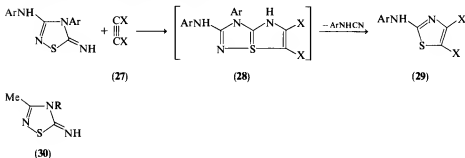
<sup>41</sup> C. P. Joshua and V. K. Verma, *Indian J. Chem.* **2**, 194 (1964).



SCHEME 3

To sum up, the addition of an unsaturated system  $X=Y=Z$  to Hector's base may be represented<sup>31,33</sup> by the reaction sequence of Scheme 3, in which the final step involves merely a proton shift, and a rotation about a C—N bond. In the case of the isothiocyanate esters, factors as yet unknown terminate the reaction at the simple addition stage **25**, but permit it to continue to **26** in the case of cyanamides and carbon disulfide. The dimethylated Hector's base does not form adducts with any of these reagents.<sup>31</sup>

With activated acetylenes (**27**,  $X = \text{PhCO}$ ,  $\text{COOMe}$ ), Hector's bases yield substituted 2-arylaminothiazoles (**29**). The course of the reaction may be rationalized by assuming the usual intermediate heteropentalene formation (**28**).<sup>42</sup> 4-Alkyl-5-imino-3-methyl- $\Delta^2$ -1,2,4-thiadiazolines (**30**) undergo the same type of reaction.<sup>43</sup>



c. *1,3-Disubstituted Thioureas*. In several extensive investigations, the oxidation of 1,3-disubstituted thioureas has been reexamined. It is re-

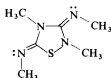
<sup>42</sup> K. Akiba, M. Ochiuni, T. Tsuchiya, and N. Inamoto, *Tetrahedron Lett.*, 459 (1975); K. Akiba, T. Tsuchiya, and N. Inamoto, *Hokusokan Kagaku Toronkai Koen Yoshishu*, 8th, 1975, 224 (1975) [*CA* **84**, 164,691m (1976)].

<sup>43</sup> K. Akiba, T. Tsuchiya, and N. Inamoto, *Tetrahedron Lett.*, 1877 (1976).

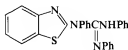
called<sup>1,3</sup> that their oxidation by hydrogen peroxide had given products that were originally formulated as substituted 1,2,4-thiadiazolidines (**31**, R = Ph), but were later identified as 2-guanidinobenzothiazoles (**33**, R = Ph). However, 1,2,4-thiadiazolidines (**31**) are in fact readily obtainable by several oxidation procedures. Thus treatment of *sym*-dialkyl(or aryl)thioureas with benzoyl peroxide (1.15 equivalents) in dichloromethane at 5–10°C provides **31** in good yields, probably by a free radical mechanism. The interesting question of the possible existence of four stereoisomeric forms of **31** was raised, but only one uniform nonseparable compound was isolated in each case (e.g., possibly **32**).<sup>44</sup>



(31)



(32)



(33)

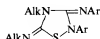
Thioureas bearing unlike substituents may yield position isomers: three (**34a–c**) of the possible four isomers that may arise from 1-alkyl-3-arylthioureas have been separated and characterized.<sup>44,45</sup> The structural type **34a** appears to predominate<sup>44</sup>; basic media favor the formation of isomers **34b**, which tend to rearrange to the more stable **34a** and/or **34c** by transient ring opening, accelerated by acids.<sup>45</sup> Interesting observations concerning 1-alkyl-3-arylthioureas containing bulky substituents exerting steric hindrance are on record,<sup>44</sup> but are too extensive to be detailed. The structural assignments based on spectral measurements, were confirmed by X-ray analyses of some typical examples (e.g., **34a**, Alk = Me, Ar = Ph<sup>44</sup>; **34b**, Alk = Et<sup>46</sup>).



(34a)



(34b)



(34c)

A technique had originally been developed for studying these oxidations in the mass spectrometer on a micro scale, using benzoyl peroxide as the oxidant. The fragmentation patterns showed that reaction proceeds as on the laboratory scale, involving the usual intermediates and producing, among other products, the expected 1,2,4-thiadiazole derivatives.<sup>47</sup>

<sup>44</sup> T. Kinoshita, S. Sato, and C. Tamura, *Bull. Chem. Soc. Jpn.* **49**, 2236 (1976).

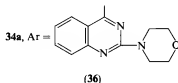
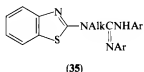
<sup>45</sup> T. Kinoshita, S. Sato, and C. Tamura, *Bull. Chem. Soc. Jpn.* **52**, 1225 (1979).

<sup>46</sup> S. Sato, T. Kinoshita, T. Hata, and C. Tamura, *Acta Crystallogr., Sect. B* **33B**, 550 (1977).

<sup>47</sup> T. Kinoshita and C. Tamura, *Tetrahedron Lett.*, 4963 (1969).



The oxidation of 1-alkyl-3-arylthioureas by sodium nitrite in ethanol-hydrochloric acid at room temperature produces 2,4-dialkyl-3,5-bis(aryl-imino)-1,2,4-thiadiazolidines (**34a**) exclusively. Here again, the structure of one member (**34a**, Alk = Me, Ar = Ph) was established by X-ray analysis. Some examples of **34a** undergo acid-catalyzed rearrangement to 2-guanidinobenzothiazoles (**35**), but others yield merely 1-alkyl-3-arylureas hydrolytically.<sup>48</sup> Similar results were obtained using hydrogen peroxide in acidified aqueous ethanol.<sup>49</sup> The familiar conversion<sup>48,50</sup> in acidic media of the resulting thiadiazolidines (**34a**) to 2-guanidinobenzothiazoles (**35**) was again observed; indeed the latter arise as by-products in the oxidation process.<sup>49</sup> This result would appear to resolve the original divergent formulations of the products (**31**, **33**; see above). The conversion by iodine in chloroform of N-substituted *N'*-(2-morpholino-4-quinazolinyl)thioureas to the thiadiazolidines (**36**, 70–90%) illustrates further the general applicability of the reaction.<sup>51</sup> An X-ray analysis of **36** gave the expected results.<sup>52</sup>



d. *Stepwise Oxidation of Thioureas.* The oxidation of thioureas in stages,<sup>3</sup> terminating in the usual final heterocyclic products (**14**, **31**, **33**, etc.), has been the subject of renewed studies (see also Sections e and f immediately below). Treatment of thioureas, bearing one to three N-substituents, with the requisite quantity of bromine or thionyl chloride yields, in the first instance, the corresponding dithioformamidine dihydrohalides (**37**).<sup>34,53,54</sup> Although they are isolable, their stability is limited: in solution, they decompose, with loss of sulfur, to the monothioformamidine dihydrohalides (**38**), or to the amidinothioureas (**39**) isomeric therewith, depending to some extent on the nature of the substituents ( $R-R^2$ ), and the experimental conditions.<sup>53,54</sup>

<sup>48</sup> C. Christophersen, T. Ottersen, K. Seff, and S. Treppendahl, *J. Am. Chem. Soc.* **97**, 5237 (1975).

<sup>49</sup> C. P. Joshua and K. N. Rajasekharan, *Aust. J. Chem.* **30**, 1819 (1977).

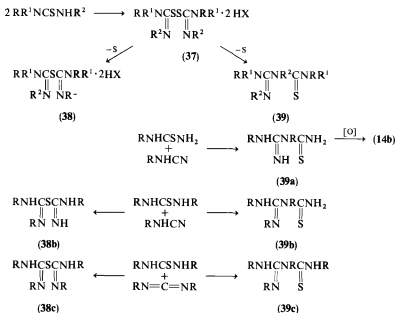
<sup>50</sup> F. Kurzer and P. M. Sanderson, *J. Chem. Soc.*, 3240 (1960).

<sup>51</sup> W. Ried, O. Moesinger, and W. Schuckmann, *Justus Liebigs Ann. Chem.*, 1817 (1977).

<sup>52</sup> W. Schuckmann, H. Fuess, O. Moesinger, and W. Ried, *Cryst. Struct. Commun.* **7**, 571 (1978).

<sup>53</sup> P. K. Srivastava, *Indian J. Chem.* **1**, 354 (1963).

<sup>54</sup> P. K. Srivastava, *Indian J. Chem.* **2**, 154 (1964).



SCHEME 4 Reference to the original literature is necessary to identify the scope and limitations of this very abbreviated scheme.

In an independent synthesis of both these isomeric products (38, 39), a (substituted) thiourea is condensed with a cyanamide or a carbodiimide (e.g., in acetone-hydrochloric acid); which of the two products predominates is controlled in some degree by a choice of suitable conditions.<sup>55,56</sup> The synthesis has been exemplified using arylcyanamides in conjunction with thiourea,<sup>56</sup> 1-alkyl-<sup>57</sup> or 1,3-dimethylthiourea<sup>57</sup> (see also Section f); it is of importance because the amidinothiureas (39) that are thus made accessible function as precursors of the 1,2,4-thiadiazolidines (31 etc.) (see Scheme 4).

The assumed<sup>3,53,54</sup> sequential occurrence of these reactions both in this synthesis and in the direct oxidation of thioureas (39 being considered an isomerization product of 38) must now be regarded as doubtful; the evidence is in better accord with the parallel independent formation of 38 and 39 (see Section e, immediately below).

The synthesis has provided additional support for the structure of Hector's base and its analogs. Thus the condensation of aromatic thioureas and

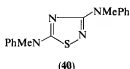
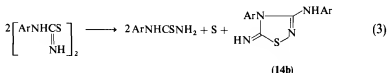
<sup>55</sup> C. P. Joshua, *J. Sci. Ind. Res., Sect. B* **21**, 588 (1962).

<sup>56</sup> S. N. Pandeya, *Indian J. Chem.* **1**, 525 (1963).

<sup>57</sup> S. N. Pandeya, *Indian J. Chem.* **2**, 440 (1964).

cyanamides produces 1-arylamidino-1-arylthioureas (**39a**)<sup>55</sup>; the substituted 1,2,4-thiadiazolidines obtained therefrom on oxidation are identical with the corresponding Hector's bases (**14b**).<sup>32</sup>

In conclusion, it is interesting that diaryldithioformamidine dihydrobromides, dissolved in acidified aqueous ethanol, may yield Hector's bases (**14b**) directly, without further addition of oxidants, according to Eq. (3). The dithioformamidine corresponding to 1-methyl-1-phenylthiourea similarly yields **40**.<sup>34</sup> Here the cyclization occurs under the influence of the excess of dithioformamidine, the oxidizing power of which is well established (e.g., liberation of iodine from iodide). Two moles of arylthiourea and one gram-atom of sulfur appear as by-products. 1-Phenylamidino-1-phenylthiourea is also oxidized by dithioformamidine to Hector's base nearly quantitatively.<sup>34</sup>



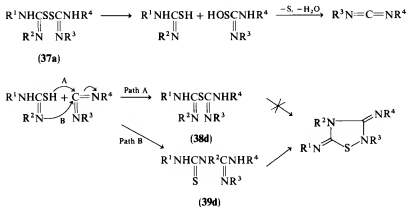
e. *Mechanism.* Based on the foregoing information, and on additional observations (see Sections f, g, below), consideration has again been given to the mechanism of the oxidation of thioureas to 1,2,4-thiadiazoles in general, and to Hector's bases in particular. The accumulated evidence favors the view that dithioformamidines and amidinothioureas function as successive intermediates in these reactions, but that monothioformamidines do not.

The ease with which two molecules of thioureas are joined by an S—S link to form dithioformamidine salts (**37**) under the influence of the most diverse oxidizing agents<sup>3,34</sup> makes it plausible that these disulfides (**37**) are the primary products of most, if not all, oxidation processes. Moreover, the disulfides (**37**) yield, on further oxidation, the same 1,2,4-thiadiazole derivatives as the thioureas from which they are derived.<sup>3</sup> Their role as the initial intermediates in the synthesis of the 1,2,4-thiadiazole ring system from thioureas is therefore generally accepted. In solution, dithioformamidine salts deposit elementary sulfur spontaneously and produce monothioformamidines (**38**) or amidinothioureas (**39**). The latter tend to predominate, and to become the sole products under more stringent conditions (e.g., on boiling). These amidinothioureas and the final 1,2,4-thiadiazoles are reversibly con-

vertible to one another by oxidation-reduction: the amidinothioureas (**39**) are therefore acknowledged<sup>3</sup> as the immediate precursors of the heterocyclic end products (**14b**).

It remains to account for the conversion of the established intermediates to one another (**37** → **39**). Consideration has been given<sup>49,53</sup> to the possible role, in this step, of the monothioformamidines (**38**), from which the amidinothioureas (**39**) were thought to arise by isomerization. It has become increasingly apparent,<sup>35,54,56,58,59</sup> however, that monothioformamidines (**38**), once formed and isolated, cannot be oxidized to 1,2,4-thiadiazoles, being recovered<sup>59</sup> or largely decomposed<sup>35,58</sup> in such attempts. In spite of their appearance as reaction products under appropriate conditions, they are unlikely to function as intermediates on the route to 1,2,4-thiadiazoles.<sup>59</sup> A more direct way in which the amidinothioureas can arise, is the scission of the dithioformamidines (**37**), with loss of sulfur, to thiourea and cyanamide (or carbodiimide)<sup>28</sup> and recombination of these fragments, as occurs in the well-established synthesis of **39** by this reaction (see Scheme 4).

The process is satisfactorily rationalized by the mechanism<sup>59</sup> shown in Scheme 5, in which the hydrolytic formation of a substituted sulfenic acid precedes that of the carbodiimide. Depending on the relative nucleophilicity of the sites in the thiourea, its condensation with carbodiimide will yield either the monosulfide (**38d**), by attack of sulfur on the carbodiimide (Path A), or the amidinothiourea (**39d**, Path B; attack by nitrogen). The distribution



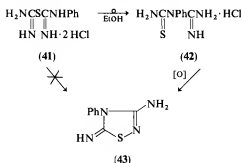
SCHEME 5

<sup>58</sup> P. K. Srivastava, *Indian J. Chem.* **7**, 323 (1969).

<sup>59</sup> A. R. Butler and I. Hussain, *J. Chem. Res. Synop.*, 407 (1980).

of the substituents ( $R^1$ – $R^4$ ) in the resulting 1,2,4-thiadiazolidine ring will be governed by the prevailing influence of the electronic and steric factors involved in reaction B.<sup>59</sup>

The reported<sup>60</sup> conversion of monothioformamidine [ $\text{NH}_2\text{C}(=\text{NH})\text{SC}(=\text{NH})\text{NH}_2$ , i.e., the parent base] to amidinothiourea by alkali can be accommodated within this mechanism by a (hydrolytic) reversal of path A, followed by recombination according to step B. However, the claim<sup>56</sup> that the dihydrochloride of the monophenyl analog (**41**) is convertible to the hydrochloride (**42**) on brief warming in ethanol appears to be difficult to reconcile with its observed inability to undergo oxidation to the 1,2,4-thiadiazole (**43**), which is readily formed from **42**.<sup>56</sup>



f. *Mixtures of Thioureas.* The behavior on oxidation of equimolar mixtures of two different thioureas<sup>61–65</sup> can also be correlated with the foregoing results. Treatment of mixtures of a 1,3-diarylthiourea and thiourea with bromine or hydrogen peroxide in acidified ethanol produces 3-amino-4-aryl-5-arylimino- $\Delta^2$ -1,2,4-thiadiazolines (**44**) (~70%), also obtainable by the same oxidation of a mixture of the corresponding dithioformamidinium salts. The involvement of “mixed” disulfides (**37a**,  $R^1, R^2 = \text{Ar}$ ;  $R^3, R^4 = \text{H}$ ) and monosulfides in the mechanism of the reaction was discussed at length, the appropriate amidinothioureas being proposed, as usual, as the immediate

<sup>60</sup> S. N. Pandeya, *Indian J. Chem.* **1**, 275 (1963).

<sup>61</sup> C. P. Joshua and P. N. K. Nambisan, *Indian J. Chem.* **11**, 1272 (1973).

<sup>62</sup> C. P. Joshua and P. N. K. Nambisan, *Indian J. Chem.* **12**, 962 (1974).

<sup>63</sup> C. P. Joshua and P. N. K. Nambisan, *Indian J. Chem.* **13**, 241 (1975).

<sup>64</sup> C. P. Joshua and P. N. K. Nambisan, *Indian J. Chem.* **14B**, 671 (1976); P. N. K. Nambisan, *Tetrahedron Lett.*, 2907 (1974).

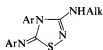
<sup>65</sup> C. P. Joshua and K. N. Rajasekharan, *Indian J. Chem.*, **14B**, 967 (1976).

precursors of the heterocyclic products (44).<sup>61</sup> Although these intermediates are not isolable in all cases by the reductive ring cleavage of the thiadiazolines (44), the molecule being fragmented further,<sup>61</sup> they are readily obtainable from thiadiazolines (45) arising from mixtures of thiourea and an 1-alkyl-3-arylthiourea, and are reconverted thereto on oxidation.<sup>62</sup> Moreover, since they are the main products, when only one equivalent of oxidant is employed, their role as intermediates is scarcely in doubt. Confirmation of their structure (and hence of that of 45) is provided by their alternative synthesis from (i) 1-alkyl-3-arylthioureas and cyanamides and (ii) thiourea and 1-alkyl-3-arylcarbodiimides.<sup>62</sup>

The oxidation of equimolar mixtures of 1,3-diarylthioureas and alkylthioureas similarly furnishes the trisubstituted 1,2,4-thiadiazolines (46).<sup>63</sup> The observations, relationships, and confirmatory syntheses resemble entirely those of the foregoing examples. Mixtures of thiourea and 1,3-diarylthioureas bearing nonidentical substituents react in such a way that the more electron-releasing aryl group (of  $\text{Ar}^1\text{NHCSNHA}r^2$ ) generally appears at the ring N-4 nitrogen of the heterocycle (47); however, the operation of steric hindrance may reverse this disposition so that 47a and 47b are formed side by side.<sup>64</sup> The work has been further amplified by the inclusion of mixtures of diarylthioureas and arylthioureas, with comparable results.<sup>65</sup>



(44) R = Ar



(46)

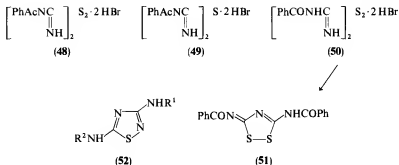


(47a)



(47b)

g. *Acylthioureas*. Only a few acylthioureas have been subjected to oxidation; although the observations on record are diverse, they can be correlated with the broad pattern established for the parent compounds. The action of bromine on 1-acetyl-1-phenylthiourea produces good yields of the substituted dithioformamidine (48) from which the monothioformamidine (49) is obtainable in the usual way. Under appropriate conditions, the oxidation continues, resulting in 3,5-bisanilino-1,2,4-thiadiazole and its monoacetyl derivative; Hector's base is obtained as a minor by-product, presumably due to partial deacetylation of the starting material. It is noteworthy that the isolated monosulfide (49) does not yield the final 1,2,4-thiadiazole on further oxidation, but is extensively decomposed, confirming once again that monosulfides are not concerned as intermediates in the overall oxidation process.<sup>58</sup>



Similarly, the oxidation of benzoylthiourea by bromine yields, in the first place, dibenzoyldithioformamidine dihydrobromide (50). On attempted recrystallization, this is converted, with loss of the elements of ammonium bromide to 5-benzoylamino-3-benzoylimino-3*H*-1,2,4-dithiazole (51) together with small quantities of 3,5-bis(benzamido)-1,2,4-thiadiazole. The preferential loss, from 50, of ammonium bromide rather than sulfur was ascribed to the influence of the benzoyl groups, and possible mechanisms were discussed.<sup>66</sup>

The oxidation of *N*-ethoxycarbonylthiourea by bromine in boiling chloroform yields a complex mixture, separable chromatographically into *N*-ethoxycarbonylurea (8%), 3,5-bis(ethoxycarbonimino)-1,2,4-dithiazolidine (29%) and three 1,2,4-thiadiazoles, viz., 52 ( $\text{R}^1 = \text{R}^2 = \text{COOEt}$ , 8%), its 2,5-bis(ethoxycarbonyl) isomer (2%), and 52 ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{COOEt}$ , 3%). Other *N*-alkoxycarbonylthioureas, as well as 1-ethoxycarbonyl-3-methylthiourea, react analogously.<sup>67</sup>

### 3. Cycloaddition of 5-Amino-1,2,3,4-thiadiazoles and Heterocumulenes

Recently a group of syntheses based on cycloadditions of 5-amino-1,2,3,4-thiadiazoles<sup>68</sup> with heterocumulenes has provided a novel general route to 1,2,4-thiadiazoles. The versatility of this approach has been demonstrated by the extensive studies of L'abbé and his co-workers since 1975.

4-Alkyl-5-arylsulfonylimino-4,5-dihydro-1,2,3,4-thiadiazoles (53) are readily accessible from alkyl azides and sulfonyl isothiocyanates.<sup>69</sup> Their thermo-

<sup>66</sup> R. L. N. Harris and L. T. Oswald, *Aust. J. Chem.* **27**, 1531 (1974).

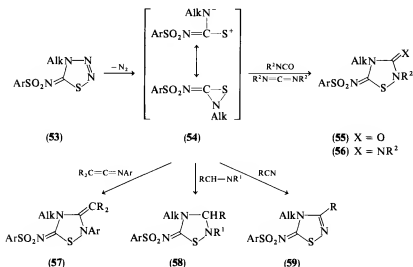
<sup>67</sup> M. Nagano, M. Oshige, T. Matsui, J. Tobitsuka, and K. Oyama, *Chem. Pharm. Bull. Jpn.* **21**, 2396 (1973).

<sup>68</sup> Review: K. A. Jensen, and C. Pedersen, *Adv. Heterocycl. Chem.* **3**, 263 (1964).

<sup>69</sup> G. L'abbé, E. van Loock, R. Albert, S. Toppet, G. Verhelst, and G. Smets, *J. Am. Chem. Soc.* **96**, 3973 (1974).

lysis yields highly reactive species (iminothiaziridines or their ring-opened dipolar isomers, (54) which undergo 1,2-addition with isocyanates or carbodiimides to afford excellent yields of the 3-oxo- (55) or 3-imino-1,2,4-thiadiazolidines (56),<sup>70,71</sup> the structure of which was confirmed by an alternative unequivocal synthesis.<sup>71</sup> The use of ketenimines similarly yields the cycloadducts (57).<sup>72</sup>

By performing the thermolysis of 53 in the presence of an equimolar amount of an anil in carbon tetrachloride, or in an excess of a nitrile at 60–70°C, the appropriate 5-tosylimino-1,2,4-thiadiazolidines (58) or 1,2,4-thiadiazolines (59) are formed in good yield.<sup>73</sup> The structure of the latter was established by an independent synthesis of a representative (59, Alk = CH<sub>2</sub>Ph, R = Ph, Ar = *p*-Tol) by Goerdeler's method,<sup>74</sup> and by an X-ray analysis.<sup>73</sup>



The use of *N*-arylsulfonylaminines as trapping agents produces substituted 3-oxo-5-arylsulfonylimino-1,3,4,2,4-dithiadiazolidines (60). On hydrolysis these are cleaved to *S*-aminoisothioureas (61), but that of the acetyl derivative (60, R = CH<sub>3</sub>CO) yields the 1,2,4-thiadiazoline (62).<sup>75</sup>

<sup>70</sup> R. Neidlein and K. Salzmann, *Synthesis*, 52 (1975).

<sup>71</sup> G. L'abbé, G. Verhelst, C. C. Yu, and S. Toppet, *J. Org. Chem.* **40**, 1728 (1975).

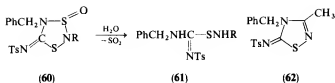
<sup>72</sup> G. L'abbé and C. C. Yu, *Chem. Ind. (London)*, 312 (1977).

<sup>73</sup> G. L'abbé, G. Verhelst, S. Toppet, G. S. D. King, and J. Briers, *J. Org. Chem.* **41**, 3403 (1976).

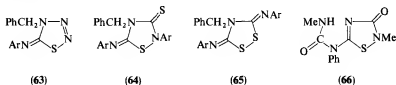
<sup>74</sup> J. Goerdeler, A. Huppertz, and K. Wember, *Chem. Ber.* **87**, 68 (1954).

<sup>75</sup> G. L'abbé, A. van Asch, J. P. Declercq, G. Germain, and M. van Meerse, *Bull. Soc. Chim. Belg.* **87**, 285 (1978).





The addition between alkyl azides and aryl isothiocyanates appears to be less clear-cut than that of arylsulfonyl isothiocyanates.<sup>69</sup> Benzyl azide reacts with 2 moles of aryl isothiocyanates at 60°C, with slow evolution of nitrogen over several days or weeks, to give no less than five products<sup>76</sup>. Although the thiadiazolidine (64) is again the major product, it gradually gives way, by isomerization, to the dithiazolidine (65) by a Dimroth rearrangement.<sup>77</sup> The observations are compatible with the operation of a mechanism involving the initial formation of 4-alkyl-5-arylimino-1,2,3,4-thiatriazolines (63), by the cycloaddition of the azide at the C=S bond of the isothiocyanate. However, there is some evidence that the next stage proceeds, not by way of the usual thiaziridines (corresponding to 54), but by a bimolecular elimination of the second molecule of isothiocyanate, with simultaneous elimination of nitrogen.<sup>76</sup>



An analogous reaction occurs with evolution of nitrogen, when 5-(substituted)amino-1,2,3,4-thiatriazoles react with isocyanate esters at room temperature, preferably in the presence of tertiary amines as catalysts. Addition of a second molecule of isocyanate tends to produce the corresponding ureas (e.g., 66).<sup>78</sup>

5-Arylimino-1,2,4-thiadiazolidin-3-ones (68) are obtained in a single operation, when a mixture of alkyl azides (4 mol) and an isocyanate ester (2 mol) is very slowly treated at 80°C with an aryl isothiocyanate (1 mol).<sup>79</sup> There is evidence that iminothiatriazolines (67) are the primary products, which react with the isocyanate ester to yield the observed products (68). Thus 4-methyl-5-phenylimino-1,2,3,4-thiatriazoline (67, R = Me, Ar = Ph),

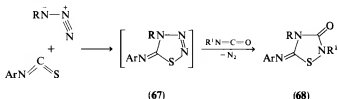
<sup>76</sup> G. L'abbé, G. Verhelst, and S. Toppet, *J. Org. Chem.* **42**, 1159 (1977).

<sup>77</sup> Review: M. Wahren, *Z. Chem.* **9**, 241 (1969); P. Guerret, R. Jacquier, and G. Maury, *J. Heterocycl. Chem.* **8**, 643 (1971).

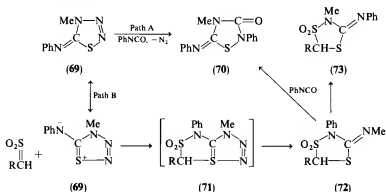
<sup>78</sup> G. Kaugars and V. L. Rizzo, *J. Org. Chem.* **44**, 3840 (1979).

<sup>79</sup> G. L'abbé and G. Verhelst, *Angew. Chem., Int. Ed. Engl.* **15**, 489 (1976).

synthesized by an independent route,<sup>80</sup> is stable up to 110°C, but reacts exothermically at room temperature with *n*-butyl isocyanate, forming **68** (*R* = Me, *Ar* = Ph, *R*<sup>1</sup> = *n*-Bu) in 95% yield, presumably by a mechanism of the type described immediately above<sup>79</sup> (see also Ref. 81).



The interaction of 4-alkyl-5-arylimino-1,2,3,4-thiatriazoline (**69**) and sulfenes (generated *in situ* from alkylsulfonyl chlorides and triethylamine<sup>82</sup>) produces sultams (**72**), possibly by way of the heteropentalenes (**71**); these isomerize above 60°C under the influence of acidic catalysts to **73**, by a Dimroth rearrangement.<sup>77</sup> The sultams (**72**) are themselves capable of acting as masked 1,3-dipoles, undergoing cycloaddition with heterocumulenes, with elimination of the sulfene moiety. Thus reaction of **72** with phenyl isocyanate produces the 1,2,4-thiadiazolidine (**70**), also directly accessible from **69** by Path A.<sup>83</sup>



In their reactivity with azides, acyl isothiocyanates occupy a position intermediate between the active arylsulfonyl and the more sluggish aryl isothiocyanates (see above). The interaction of alkyl azides and benzoyl

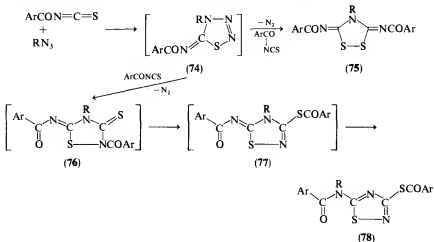
<sup>80</sup> R. Neidlein and J. Tauber, *Arch. Pharm. (Weinheim, Ger.)* **304**, 687 (1971).

<sup>81</sup> G. L'abbé, E. van Loock, G. Verhelst, and S. Toppet, *J. Heterocycl. Chem.* **12**, 607 (1975).

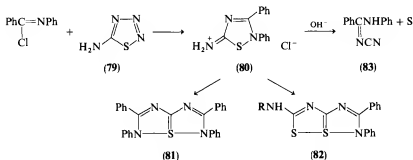
<sup>82</sup> Review: G. Opitz, *Angew. Chem., Int. Ed. Engl.* **6**, 107 (1967); J. F. King, *Acc. Chem. Res.* **8**, 10 (1975).

<sup>83</sup> G. L'abbé, A. Timmerman, C. Martens, and S. Toppet, *J. Org. Chem.* **43**, 4951 (1978).

isothiocyanate (2 mol, in chloroform, 45°C, 11 days) yields the 3-arythio-1,2,4-thiadiazoles (**78**) as main products. X-Ray analysis of one member of the series (**78**, Ar = Ph, R = *n*-C<sub>4</sub>H<sub>9</sub>) established their structure. The dithiazolidines (**75**), usually forming very minor by-products, may in some examples become more prominent. The reaction is thought to involve the usual initial formation of the cyclo adduct (**74**; so far not isolated), which reacts with the second molecule of isothiocyanate at its C=N and/or C=S bond. The ultimate formation of the stable aromatic 1,2,4-thiadiazole (**78**) presupposes **76** to undergo two rearrangements (possibly **76** → **77** → **78**).<sup>84</sup>



5-Amino-1,2,3,4-thiatriazole (**79**) itself has also been employed in these studies. Its interaction with an equimolar amount of *N*-phenylbenzimidoyl

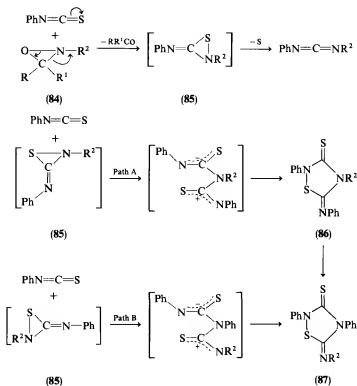


<sup>84</sup> G. L'abbé, M. Komatsu, C. Martens, S. Toppet, J. P. Declercq, G. Germain, and M. Van Meerssche, *Bull. Soc. Chim. Belg.* **88**, 245 (1979).

chloride in the absence of base yields the 5-imino-1,2,4-thiadiazolium salt (**80**) as the sole product. This is capable of reacting, in pyridine, with another molecule of the imidoyl chloride, or with an isothiocyanate ester, to yield the 6aλ<sup>4</sup>-thiapentalenes (**81**, **82**). Alkaline hydrolysis cleaves **80** quantitatively to **83** and sulfur.<sup>85</sup>

#### 4. Cycloadditions of Oxaziridines and Isothiocyanates

The interaction of oxaziridines (**84**) and phenyl isothiocyanate is also rationalized in terms of the formation of iminothiaziridines (**85**) as the reactive intermediates (see Section II.A,3). The reaction yields carbodiimides, but produces the 1,2,4-thiadiazolidines **86** and/or **87** under mild conditions, probably by a mechanism outlined in Scheme 6. Members of series **86** are



SCHEME 6

<sup>85</sup> G. L'abbé, G. Verhelst, and G. Vermeulen, *Angew. Chem., Int. Ed. Engl.* **16**, 403 (1977).

isomerized to those of **87** in good yield in boiling benzene in the presence of catalytic amounts of triethyl phosphite. 2-*tert*-Butyloxaziridine behaves exceptionally in producing an oxadiazolidinethione, probably for steric reasons.<sup>86</sup>

### 5. Cycloaddition of Dithiazoles and Heterocumulenes

The interconvertibility of 1,2,4-dithiazoles and 1,2,4-thiadiazoles has been known for a long time. Examples of such reactions have been encountered in the study of "isoperthiocyanic acid" (3-imino-1,2,4-dithiazolidine-5-thione) and its analogs (the "thiurets", "isothiocyanate oxides and sulfides"), and their elucidation has not been as easy matter.<sup>1,3</sup> The interpretation of these, and of novel conversions of 1,2,4-dithiazoles to 1,2,4-thiadiazoles has more recently been greatly aided by the application of physical methods, including X-ray analyses. Since the reactions are not all of one kind, it has been expedient to describe them in two separate Sections, among the syntheses of type A and type C, respectively.

A novel group of reactions of the first type is the condensation of 1,2,4-dithiazoles with heterocumulenes, which provides a route to a variety of reduced 1,2,4-thiadiazole derivatives. Thus, 5-ethoxy-3-phenylimino-3*H*-1,2,4-dithiazole (**89**) (readily obtainable from **88** as shown) reacts with isocyanate esters to yield 2-substituted 5-(ethoxythiocarbonyl)imino-4-phenyl-1,2,4-thiadiazolidin-3-ones (**91**).<sup>87</sup> The reaction may be visualized to proceed by the [3 + 2] cycloaddition of the (S—S) ring-opened dithiazole and the heterocumulene<sup>87</sup>; in accordance with analogous cases, the intermediate formation of a heteropentalene (**90**) might be postulated. Further examples of this general reaction are outlined in Scheme 7.<sup>88</sup> An X-ray analysis<sup>89</sup> has confirmed the structure of the product of the condensation of **92** and phenyl isothiocyanate<sup>90</sup> as the 1,2,4-thiadiazolidine **94** (R = Ph), thus excluding the possible alternative dithiazole structure (**94b**), which is indeed taken up by the products of analogous condensations.<sup>91,92</sup> The use

<sup>86</sup> M. Komatsu, Y. Ohshiru, K. Yasuda, S. Ichijima, and T. Agawa, *J. Org. Chem.* **39**, 957 (1974).

<sup>87</sup> J. Goerdeler, W. Kunnes, and F. M. Panshri, *Chem. Ber.* **109**, 848 (1976).

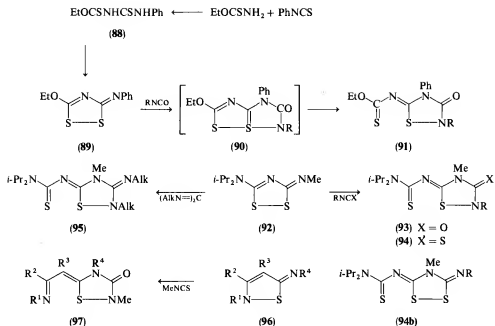
<sup>88</sup> J. Goerdeler, R. Buechler and S. Sólyom, *Chem. Ber.* **110**, 285 (1977).

<sup>89</sup> L. K. Hansen, *Acta Chem. Scand., Ser. A* **A31**, 855 (1977).

<sup>90</sup> J. Goerdeler and J. Ulmen, *Chem. Ber.* **105**, 1568 (1972); J. Goerdeler, *Lect., Int. Congr. Heterocycl. Chem., 4th, 1973* (Quoted in Ref. 88).

<sup>91</sup> J. E. Oliver and R. T. Brown, *J. Org. Chem.* **39**, 2228 (1974).

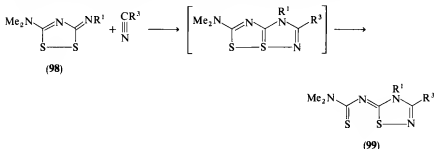
<sup>92</sup> J. E. Oliver, J. L. Flippen, and J. Karle, *Chem. Commun.*, 1153 (1972); J. L. Flippen, *J. Am. Chem. Soc.* **95**, 6073 (1973).



SCHEME 7

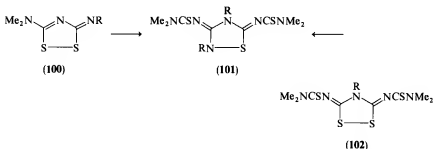
of an iminoisothiazole (96) as the starting material,<sup>88</sup> though not strictly within the scope of this Section, is noteworthy. As for comparable structures, possible interactions between the linear triads S—S—N (in 93 and 95) and N—S—N (in 97) were considered and discussed.<sup>88</sup>

In the alkylation of 5-dialkylamino-3-imino-1,2,4-dithiazoles (98), the occasional use of acetonitrile as solvent resulted in its 1,3-dipolar addition to the heterocycle, yielding 1,2,4-thiadiazoles (99) as the minor products.<sup>93</sup>

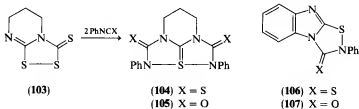


<sup>93</sup> J. E. Oliver and A. B. DeMilo, *J. Org. Chem.* **39**, 2225 (1974).

The thermal decomposition of 5-dialkylamino-3-alkylimino-1,2,4-dithiazoles (**100**) gives products derived from two molecules of the reactant, with loss of one atom of sulfur. They were formulated as substituted 3,5-bis(thioureido)-1,2,4-thiadiazolidines (**101**), and were thought to arise by a mechanism involving intermediate spirans.<sup>94</sup> They were also obtained from the thioureido-1,2,4-dithiazoles (**102**) by successive alkylation and aminolysis.<sup>95</sup> An X-ray analysis has confirmed the structure of **101** (R = Me) in its solid state.<sup>96</sup>



Condensed ring systems incorporating the 1,2,4-thiadiazole nucleus are also accessible by this reaction.<sup>97</sup> Thus 5,6-dihydropyrimido[2,1-*c*]-1,2,4-dithiazole-3[7*H*]-thione (**103**) reacts with two moles of phenyl isothiocyanate in benzene at room temperature to yield a symmetrical product formulated as the 3,4-propano-6 $\lambda^4$ -thia-1,3,4,6-tetraazapentalene (**104**). Its oxo analog (**105**) obtained by the use of phenyl isocyanate, gives rise to an intense broad carbonyl peak in its IR spectrum, which confirms the formulation unambiguously. The heteropentalenes (**104**, **105**) are well defined stable compounds, the structures of which have, according to their NMR spectra, real or time-averaged symmetry in solution. The nature of these structures, and their relation to the heteropentalenes of the thiathiophthen type was



<sup>94</sup> J. E. Oliver and J. L. Flippen, *J. Org. Chem.* **39**, 2233 (1974).

<sup>95</sup> J. E. Oliver, *J. Org. Chem.* **39**, 2235 (1974).

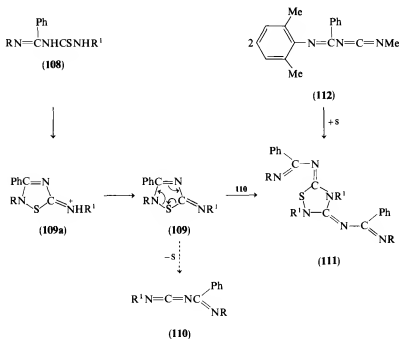
<sup>96</sup> J. L. Flippen, *Phosphorus Sulfur* **3**, 185 (1977).

<sup>97</sup> R. J. S. Beer and A. Naylor, *Tetrahedron Lett.*, 2989 (1973); R. J. S. Beer, N. H. Holmes, and A. Naylor, *J. C. S. Perkin I*, 2909 (1979).

discussed. Members of the benzimidazo[2,1-*b*]-1,2,4-thiadiazole system (e.g., **106**, **107**) were also described.<sup>97</sup>

## 6. Syntheses from 5-Imino- $\Delta^3$ -1,2,4-thiadiazolines

5-Imino- $\Delta^3$ -1,2,4-thiadiazolines (**109**) undergo various cycloadditions with heterocumulenes and unsaturated molecules as well as a remarkable self-condensation. All these involve ring cleavage and formation of new 1,2,4-thiadiazole rings and may be regarded formally as thiadiazole syntheses of type A.<sup>98,99</sup> The reactants are readily accessible as stable salts (**109a**) by oxidative cyclization of imidoylthiureas (**108**) (see Type C synthesis, Section II,C,1,a).<sup>98</sup> The free bases (**109**), however, are generally unstable, particularly those bearing an alkyl substituent in their exocyclic 5-imino group: two molecules undergo condensation spontaneously, with loss of sulfur and formation of the new substituted 1,2,4-thiadiazolidines (**111**).<sup>99</sup> Their possible alternative formulation as isomers of **111** is discounted on the basis of <sup>13</sup>C-NMR measurements.<sup>99</sup>



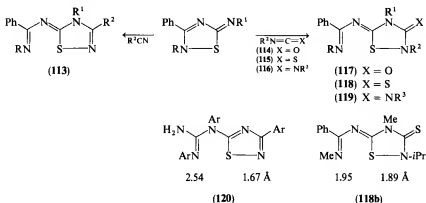
<sup>98</sup> J. Goerdeler and W. Loebach, *Chem. Ber.* **112**, 517 (1979).

<sup>99</sup> J. Goerdeler, J. Haag, and W. Loebach, *Chem. Ber.* **112**, 1288 (1979).



The condensation (**109**  $\rightarrow$  **111**) appears to involve the initial desulfurization of **109** to the imidoilcarbodiimides (**110**), which condense with **109**, as yet unreacted, to give the observed products (**111**). Indeed, the separate interaction of these two components (**109**, **110**) yields the same 1,2,4-thiadiazolidines (**111**), as does the base-catalyzed condensation of two moles of the imidoilcarbodiimide (**112**) with one of sulfur.<sup>99</sup> The condensation (**109**  $\rightarrow$  **111**) resembles that of certain comparable imino-1,2,4-dithiazoles (see Section II.C.2). The ready loss of sulfur from the 5-imino- $\Delta^3$ -1,2,4-thiadiazolines (**109**) may occur by the mechanism suggested: it is noteworthy that their 5-imino- $\Delta^2$  isomers,<sup>100</sup> which cannot eliminate sulfur in this way, are stable.<sup>99</sup>

Analogous base-catalyzed condensations of the 5-imino- $\Delta^3$ -1,2,4-thiadiazolines (**109**) with heterocumulenes such as isothiocyanate esters or carbodiimides (**114**–**116**) produce the 1,2,4-thiadiazolidines (**117**–**119**), while the addition of nitriles results in the 1,2,4-thiadiazolines (**113**).<sup>98</sup> The structural assignments are in accord with the spectral properties of the products and receive further support from an X-ray analysis of **118b**. In this structure, the near identity of the interatomic distances of the linear N—S—N triad, and their difference from the normal N—S value (1.76 Å), indicate the existence of no-bond interaction by  $\sigma$ -delocalization. The corresponding molecular dimensions of a structurally comparable “true” 1,2,4-thiadiazole (**120**)<sup>101</sup> reinforce this interpretation.<sup>98</sup>



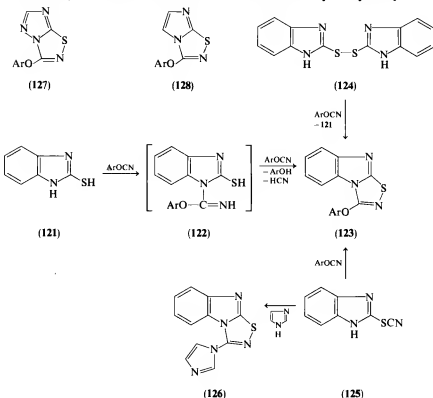
## 7. Condensation of Thioamides and Cyanate Esters

Heterocyclic compounds bearing a mercapto group ortho to a ring nitrogen react with aromatic cyanate esters (2 mol) to yield fused structures

<sup>100</sup> J. Goerdeler and W. Roth, *Chem. Ber.* **96**, 534 (1963).

<sup>101</sup> K. Akiba, T. Tsuchiya, and N. Inamoto, *Chem. Lett.*, 723 (1976).

incorporating a 1,2,4-thiadiazole ring. 2-Mercaptobenzimidazole (**121**), for example, gives rise to benzimidazolo[1,2-*d*]-1,2,4-thiadiazoline derivatives (**123**) in satisfactory yields. The reaction proceeds by way of intermediate isoureas (**122**) which are isolable in small quantities in certain examples.<sup>102</sup> They are cyclized to **123** by the second molecule of cyanate, which is itself converted to phenol and hydrogen cyanide. Imidazolo [1,2-*d*]-1,2,4-thiadiazolines (**128**) and comparable ring systems (e.g., **127**) are similarly accessible. In closely related reactions, **123** arises when 2-thiocyanatobenzimidazole (**125**) or the disulfide (**124**) are condensed with aryl cyanates.<sup>102,103</sup> 2-Thiocyanatobenzimidazole (**125**) also condenses with imidazole in acetone with remarkable ease to yield unexpectedly 1,2,4-thiadiazolo[4,5-*a*]benzimidazole (**126**),<sup>104</sup> the structure of which was established by X-ray analysis.<sup>105</sup>



<sup>102</sup> D. Martin, A. Wenzel, and R. Bacaloglu, *J. Prakt. Chem.* **320**, 677 (1978).

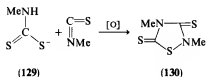
<sup>103</sup> D. Martin and A. Wenzel, German (East) Patent 133,675 (1979) [*CA* **91**, 123,737g (1979)].

<sup>104</sup> R. D. Haugwitz and V. L. Narayanan (to Squibb & Son), U.S. Patent 3,864,353 (1975) [*CA* **82**, 156,323m (1975)].

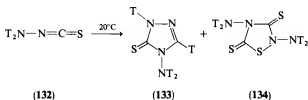
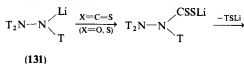
<sup>105</sup> R. D. Haugwitz, B. Toeplitz, and J. Z. Gougoutas, *J. C. S. Chem. Commun.*, 736 (1977).

8. *Syntheses from Isothiocyanate Esters*

Aqueous solutions of methyl isothiocyanate (0.1 *M*) slowly deposit 2,4-dimethyl-1,2,4-thiadiazolidine-3,5-dithione (**130**). The dithiocarbamate (**129**) is a probable intermediate in this reaction: its concentration slowly rises to detectable levels, reaching a maximum of 5% of that of the initial methyl isothiocyanate, and declines as **130** appears. The thiadiazolidine is thought to arise from the components by air oxidation: exclusion of oxygen stops the process.<sup>106</sup>



A similar observation concerns bis(trimethylsilyl)amino isothiocyanate (**132**), which is obtainable from lithium tris(trimethylsilyl)hydrazide (**131**) as shown. It is a labile compound which changes slowly at room temperature to two products (75% after 10 days), one of which has been tentatively represented as 2,4-bis(trimethylsilyl)amino-1,2,4-thiadiazolidine-3,5-dithione (**134**).<sup>107</sup>



The interaction of ethyl isothiocyanate and antimony pentachloride in carbon tetrachloride gives a complex (recrystallizable from 1,2-dichloromethane) of composition  $\text{C}_6\text{H}_{10}\text{N}_2\text{S}_2\text{Cl}^+ \text{SbCl}_6^-$ . The structure of its organic moiety may be that of the 1,2,4-thiadiazoline cation (**135**), but the evidence is not conclusive.<sup>108</sup>

<sup>106</sup> G. J. Bridgman and I. R. Wilson, *Aust. J. Chem.* **24**, 2695 (1971).

<sup>107</sup> N. Wiberg and G. Huebler, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **33B**, 575 (1978).

<sup>108</sup> G. J. Goetz-Grandmont and M. J. F. Leroy, *J. Inorg. Nucl. Chem.* **39**, 1527 (1977).



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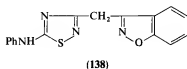
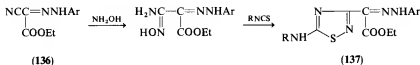
A synthesis of Type A involving N-substituted S-chloroisothiocabamoyl chlorides is described in conjunction with other synthetic applications of these reagents (see Section II,B,4,c).

## B. TYPE B SYNTHESSES



### 1. Syntheses from Amidoximes

Thiemann's classical synthesis of 1,2,4-thiadiazoles<sup>3</sup> from amidoximes continues to be used occasionally for preparative purposes. 1,2,4-Thiadiazoles of type 137, for example, arise from ethyl cyanoglyoxalate arylhydrazones (136) by the successive action of hydroxylamine and isothiocyanate esters.<sup>109</sup> The heteryl-substituted 1,2,4-thiadiazole 138 has been obtained similarly.<sup>110</sup>



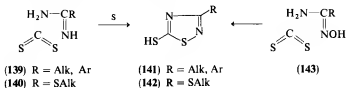
(138)

A reaction that is formally comparable to Thiemann's synthesis of 5-mercapto-1,2,4-thiadiazoles (141) from amidoximes (143) is the condensation

<sup>109</sup> R. G. Dubenko and P. S. Pelkis, USSR Patent 170,994 (1965) [*CA* **63**, 9868 (1965)]; R. G. Dubenko, E. F. Gorbenko, V. D. Panchenko, and P. S. Pelkis, *Khim. Geterotsikl. Soedin.*, 740 (1969) [*CA* **72**, 31,704y (1970)].

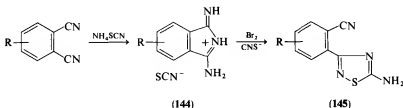
<sup>110</sup> H. Uno, M. Kurokawa, K. Natsuka, Y. Yamato, and H. Nishimura, *Chem. Pharm. Bull.* **24**, 632 (1976).

of amidines with carbon disulfide in methanol–dimethylformamide in the presence of sodium methylate and 1–2 equivalents of sulfur.<sup>111</sup> Amidines (139)<sup>111,112</sup> or isothioureas (140)<sup>111</sup> are thus converted to the corresponding 3-alkyl(or aryl) (141) or 3-alkylthio compounds (142) in high yield. The sulfur appears to act as the dehydrogenating agent: in its absence the reaction gives thioamides and amidinium thiocyanate. The conversion of cyanamide to the dipotassium salt of 3,5-dimercapto-1,2,4-thiadiazole (perthiocyanic acid) is another variant of this synthesis.<sup>113</sup>



## 2. Synthesis from N-Thiocyanatoamidines

Goerdeler's general synthesis<sup>3</sup> of 5-amino-1,2,4-thiadiazoles by the cyclization of *N*-thiocyanatoamidino compounds formed *in situ* has been further exploited.<sup>114–116</sup> 1-Amino-3-iminoisoindoleninium thiocyanates (144), which are accessible from *o*-dinitriles, can function as the amidine, and yield, by the usual simultaneous action of bromine and sodium methoxide,<sup>117</sup> or of sodium hypobromite,<sup>118</sup> 3-substituted 5-amino-1,2,4-thiadiazoles (145).



<sup>111</sup> Badische Anilin und Soda Fabrik A. G., British Patent 1,116,198 (1968) [CA 69, 86,998r (1968)].

<sup>112</sup> Y. E. Moharir, *Indian J. Chem.* **10**, 315 (1972).

<sup>113</sup> S. J. Brois and A. Gutierrez (to Exxon Research and Engineering Co.), German Patent 2,608,217 (1976) [CA 86, 55,452e (1977)].

<sup>114</sup> W. H. Moore, E. B. Towne, and J. B. Dickey (to Eastman Kodak Co.), U.S. Patents 3,221,006 (1965), 3,272,791 (1966) [CA 65, 10,701, 18,728 (1966)].

<sup>115</sup> Eastman Kodak Co., French Patent 1,456,265 (1966) [CA 67, 109,606m (1967)].

<sup>116</sup> T. Konotsune and T. Yanai (to Sankyo Co.), Japanese Patent 18,899 (1974) [CA 80, 133,446y (1974)].

<sup>117</sup> K. Leverenz, *Angew. Chem.* **85**, 226 (1973).

<sup>118</sup> K. Leverenz (to Bayer A.G.), German Patent 2,106,585 (1972) [CA 77, 166,153s (1972)].

### 3. *Syntheses from Amidino Compounds and Halogenated Methyl Mercaptans*

The ingenious general synthesis of 1,2,4-thiadiazoles from amidino compounds and tri-, di-, and monochloromethanesulfonyl chlorides has been employed repeatedly since its original development by Goerdeler and his co-workers.<sup>3,119</sup> By far the greatest number of these applications has involved the use of the fully chlorinated methyl mercaptan, resulting in 5-chloro-1,2,4-thiadiazoles.

a. *Trichloromethanesulfonyl Chloride* ("Perchloromethyl Mercaptan"). The conversion of amidines to 3-substituted 5-halogeno-1,2,4-thiadiazoles has been repeatedly described.<sup>120-124</sup> 5-Chloro-3-trichloromethyl-1,2,4-thiadiazole is readily accessible from trichloroacetimidine by this route<sup>125-128</sup>; it has attained significant economic importance as the most convenient starting material for producing the widely used pesticide 5-ethoxy-3-trichloromethyl-1,2,4-thiadiazole<sup>127,129-131</sup> (see Section V) and analogous products.<sup>125,129,130</sup> A number of 3-alkylthio-5-chloro-1,2,4-thiadiazoles have again been produced by this synthesis, using S-alkylisothiourcas.<sup>132-134</sup>

<sup>119</sup> J. Goerdeler, H. Groschopp, and U. Sommerlad, *Chem. Ber.* **90**, 182 (1957).

<sup>120</sup> I. Saikawa and A. Takai, *Yakugaku Zasshi* **85**, 948 (1964) [*CA* **64**, 5073 (1966)]; I. Saikawa and T. Wada, Japanese Patent 2,353 (1967) [*CA* **66**, 95,053u (1967)].

<sup>121</sup> H. Berger, R. Gall, H. Merdes, K. Stach, W. Sauer, and W. Voemel (to Boehringer Mannheim G.m.b.H.), German Patent 2,030,218 (1971) [*CA* **76**, 72,536w (1972)].

<sup>122</sup> J. Krenzer and S. B. Richter (to Velsicol Chemical Corp.), U.S. Patent 3,720,684 (1973) [*CA* **79**, 5343e (1973)].

<sup>123</sup> H. Roehling and G. Hoerlein, *Justus Liebigs Ann. Chem.*, 504 (1974).

<sup>124</sup> W. J. Ross, J. P. Verge, and W. R. N. Williamson (to Lilly Industries), German Patent 2,625,285 (1976) [*CA* **86**, 140,055x (1977)].

<sup>125</sup> V. L. Narayanan, J. Bernstein, and J. Williams, *J. Pharm. Sci.* **55**, 217 (1966).

<sup>126</sup> V. L. Narayanan and J. Bernstein (to Olin Mathieson Chemical Corp.), U.S. Patent 3,287,464 (1966) [*CA* **66**, 65,479v (1967)].

<sup>127</sup> J. Bernstein (to Olin Mathieson Chemical Corp.), U.S. Patent 3,324,141 (1967) [*CA* **67**, 73,611t (1967)].

<sup>128</sup> P. M. Pivawer and D. A. Farmer (to Olin Corp.), German Patent 2,519,315 (1975) [*CA* **84**, 164,860r (1976)].

<sup>129</sup> Olin Mathieson Chemical Corp., French Patent 1,339,238 (1963) [*CA* **60**, 5513 (1964)].

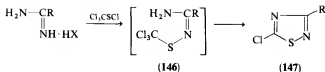
<sup>130</sup> H. Schroeder (to Olin Mathieson Chemical Corp.), U.S. Patent 3,260,588 (1966) [*CA* **65**, 12,212 (1966)].

<sup>131</sup> J. A. Wojtowicz and S. K. Bhutani (to Olin Corp.), U.S. Patent 3,890,338 (1975); D. F. Gavin (to Olin Corp.), U.S. Patent 3,890,339 (1975) [*CA* **83**, 164,192-3e (1975)].

<sup>132</sup> J. A. Stephens (to Monsanto Co.), U.S. Patent 3,159,644 (1964) [*CA* **62**, 7769 (1965)].

<sup>133</sup> J. Mostecky and V. Rabl, *Sb. Vys. Sk. Chem. Technol. Praze, Technol. Paliv* **9**, 31 (1966) [*CA* **66**, 94,961b (1967)].

<sup>134</sup> T. Kuwamura, H. Ando, and Y. Minegishi, *Yakugaku* **25**, 47 (1976).



The surmise that trichloromethylsulfenamides (146) function as intermediates in these reactions,<sup>3,119</sup> has been confirmed by the isolation and characterization of such derivatives from amidines forming part of a heterocyclic system (e.g., 148); 5-amino-1,2,4-thiadiazoles themselves yield such derivatives.<sup>135</sup> The isolated trichloromethylsulfenamide heterocyclics react with primary amines to form condensed ring systems incorporating the 1,2,4-thiadiazole structure.<sup>136</sup> 2-Trichloromethylsulfenamido pyrimidine (148), for example, reacts with a variety of primary arylamines in chloroform, giving moderate yields of 3*H*-1,2,4-thiadiazolo[4,3-*a*]pyrimidines (149). Their spectral properties exclude their possible alternative formulation as 150.<sup>136</sup> (For a conversion 149 → 150, see immediately below). The same approach gave members of the following ring systems<sup>136,137</sup>: 3*H*-1,2,4-thiadiazolo[4,3-*c*]pyrimidines (from 4-aminopyrimidine); 3*H*-1,2,4-thiadiazolo[4,3-*a*]pyrazines (from 2-aminopyrazine); 3*H*-1,2,4-thiadiazolo[4,3-*b*]pyridazines (from 2-amino-6-chloropyridazine)<sup>136,137</sup>; and 3*H*-1,3,4-thiadiazolo[2,3-*c*]-1,2,4-thiadiazoles (from 2-amino-1,3,4-thiadiazoles),<sup>138</sup> as well as isolated examples of some others.<sup>138</sup>



(148)



(149)



(150)

The reaction may be performed in one stage by preparing the trichloromethylsulfenamido heterocycle *in situ* in the presence of an aromatic amine: 1,2,4-thiadiazolo[4,3-*a*]pyridine derivatives (152), for example, have been produced in this way.<sup>139</sup> Suitable enolate ions, e.g., acetylacetone or diethyl malonate, give rise to compounds of type 155,<sup>140</sup> probably by the successive displacement (from 151) of a chloride ion, loss of hydrogen chloride, and cyclization of the resulting  $\alpha,\beta$ -unsaturated intermediate 154 by a Michael-

<sup>135</sup> J. Goerdeler and E. R. Ehrbach, *Chem. Ber.* **95**, 1637 (1962).

<sup>136</sup> K. T. Potts and J. Kane, *J. Org. Chem.* **38**, 3087 (1973).

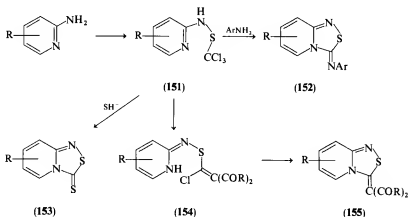
<sup>137</sup> J. M. Kane, *Diss. Abstr. Int. B* **36**, 3388 (1976) [*CA* **84**, 164,690k (1976)].

<sup>138</sup> J. O. Gardner and C. C. Beard, *J. Pharm. Sci.* **68**, 182 (1979).

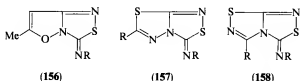
<sup>139</sup> K. T. Potts and R. Armbruster, *J. Org. Chem.* **35**, 1965 (1970).

<sup>140</sup> K. T. Potts and R. Armbruster, *J. Org. Chem.* **36**, 1846 (1971).

type addition of the pyridine moiety. The action of hydrosulfide ion on **151** produces 3*H*-1,2,4-thiadiazolo[4,3-*a*]pyridine-3-thiones (**153**).<sup>140,141</sup>



The same route afforded the following condensed ring systems<sup>142</sup>: 3*H*-isoxazolo[3,2-*c*]-1,2,4-thiadiazoles (**156**); 3*H*-1,2,4-thiadiazolo[3,4-*b*]-1,3,4-oxadiazoles; 3*H*-thiazolo[2,3-*c*]-1,2,4-thiadiazoles; 3*H*-1,3,4-thiadiazolo[2,3-*c*]-1,2,4-thiadiazoles (**157**); and 3*H*-1,2,4-thiadiazolo[4,3-*d*]-1,2,4-thiadiazoles (**158**).<sup>142</sup>



3*H*-1,2,4-Thiadiazolo[4,3-*a*]pyridines (**152**, e.g., Ar = 2-pyridyl) are photochemically stable: no photolytic products are formed by the action of ultraviolet light, the absorbed energy being emitted as fluorescence, generally in high quantum yield. Detailed studies are available of their fluorescence spectra in isotropic solvents,<sup>143</sup> and of their fluorescence behavior as guest molecules in aligned nematic liquid crystals [of *N*-(*p*-methoxybenzylidene)-*p*-butylaniline].<sup>144</sup>

The 3-substituted 3*H*-1,2,4-thiadiazolo[4,3-*a*]pyrimidine (**149**, R = 2-pyridyl) undergoes a rearrangement of the Dimroth type<sup>77</sup> in 10% ethanolic

<sup>141</sup> R. F. Armbruster, *Diss. Abstr. Int.*, **B 32**, 3246 (1971) [*CA* **76**, 99,590w (1972)].

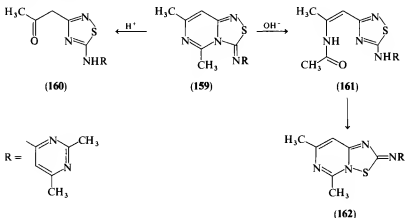
<sup>142</sup> K. T. Potts and J. Kane, *J. Org. Chem.*, **40**, 2600 (1975).

<sup>143</sup> K. T. Potts, H. H. Richtol, and R. Armbruster, *Anal. Chem.*, **43**, 1304 (1971).

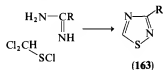
<sup>144</sup> W. F. Wezel and H. H. Richtol, *Mol. Cryst. Liq. Cryst.*, **47**, 51 (1978).



hydrochloric acid, or sodium hydroxide, yielding **150**, the structure of which is supported by its alternative synthesis from the appropriate amidinothiourea by oxidative cyclization. In contrast, the isomeric 1,2,4-thiadiazolo-[4,3-*c*]pyrimidine system (e.g., **159**) does not give rearranged products, but is cleaved to the 3-acetyl derivative **160** on treatment with acid, and to **161** with alkali. The latter reaction involves the addition of the elements of water to the starting material, and is a rare example of the isolation of a Dimroth intermediate. It is cyclized to **162** by boiling phosphorus oxychloride.<sup>137,145</sup>



b. *Dichloromethanesulfonyl Chloride*. The use of dichloromethanesulfonyl chloride in this synthesis provides a direct route to 1,2,4-thiadiazoles unsubstituted in their 5-position.<sup>146</sup> 3-Benzhydrylmercapto-1,2,4-thiadiazole (**163**,  $\text{R} = \text{SCHPh}_2$ ) has been prepared from *S*-benzhydrylisothiurea by this method, but yields are low (7%).<sup>147</sup>



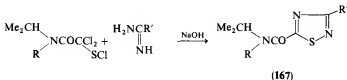
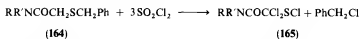
Functionalized dichloromethylsulfonyl chlorides ( $\text{XCl}_2\text{CSCl}$ ) will clearly give rise to 5-substituted analogs:  $\alpha$ -carbamoyl- $\alpha,\alpha$ -dichlorosulfonyl chlorides (**165**), for example, which have become available by chlorination ( $\text{SO}_2\text{Cl}_2$ )

<sup>145</sup> K. T. Potts and J. Kane, *J. Org. Chem.* **39**, 3783 (1974).

<sup>146</sup> J. Goerdeler and M. Budnowski, *Chem. Ber.* **94**, 1682 (1961).

<sup>147</sup> J. Goerdeler and I. El Tom, *Chem. Ber.* **98**, 1544 (1965).

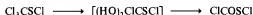
of benzyl sulfides (164)<sup>148</sup> or mercaptoacetanilides (166)<sup>149,150</sup> react with amidines, to afford 3-substituted 5-carbamoyl-1,2,4-thiadiazoles (167), albeit in moderate yields (13–42%).<sup>149,150</sup>



#### 4. Syntheses from Amidines and Chlorothioformyl Chlorides

A novel group of syntheses developed in the early 1970s employs chlorothioformyl chloride and its analogs for supplying the S—C moiety of the 1,2,4-thiadiazole ring. Cyclization occurs with the usual range of structures which possess an actual or potential amidino grouping and may be regarded as a logical extension of the general route described in the foregoing Section.

a. *Chlorothioformyl Chloride (Chlorocarbonylsulfenyl Chloride).* Chlorothioformyl chloride is accessible by treatment of trichloromethanesulfenyl chloride with nearly concentrated sulfuric acid at 45–50°C, until the evolution of hydrogen chloride ceases.<sup>151</sup>



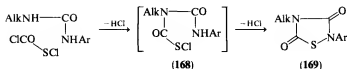
The condensation of chlorothioformyl chloride and 1-alkyl-3-arylgureas occurs in boiling benzene and affords 4-alkyl-2-aryl-1,2,4-thiadiazolidine-3,5-diones (169) in high yield. The alkylamino group of the ureas is thought to be attacked preferentially, leading to the formation of intermediates of type 168.<sup>151</sup>

<sup>148</sup> W. G. Phillips and K. W. Ratts, *J. Org. Chem.* **36**, 3145 (1971).

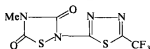
<sup>149</sup> W. G. Phillips and K. W. Ratts, *J. Org. Chem.* **37**, 1526 (1972).

<sup>150</sup> W. G. Phillips (to Monsanto Co.), U.S. Patent 3,770,749 (1973) [*CA* **80**, 48,004h (1974)]; U.S. Patent 3,859,296 (1975) [*CA* **82**, 98,007y (1975)].

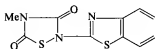
<sup>151</sup> G. Zumach, L. Eue, W. Weiss, E. Kuehle, and H. Hack (to Bayer A. G.), British Patent 1,115,350 (1968) [*CA* **69**, 96,732 (1968)]; South African Patent 7491 (1968) [*CA* **70**, 47,465r (1969)].



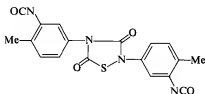
Numerous examples of this series, many containing a 2-hetero substituent, were prepared by this route,<sup>152-156</sup> chiefly because of their selective herbicidal properties, and their potential value in the cultivation of grain and cotton. The structural types described included **170**,<sup>152</sup> **171**,<sup>155</sup> and **172**.<sup>156</sup> The bis-1,2,4-thiadiazole system **173** was obtained from 1-methyl-3-(1,2,4-thiadiazol-5-yl) urea.<sup>157</sup> S-Alkylisothioureas give rise to 3-alkylthio-5-hydroxy-1,2,4-thiadiazoles.<sup>158</sup>



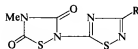
(170)



(171)



(172)



(173)

The use of cyanamides and carbodiimides in this reaction is also on record. Isopropylcyanamide undergoes an addition-substitution with chlorothioformyl chloride, resulting in 3-chloro-4-isopropyl- $\Delta^2$ -1,2,4-thiadiazolin-5-one (**174**). The use of fluorothioformyl chloride produces **174** and **175** side

<sup>152</sup> D. Ruecker, C. Metzger, and L. Eue (to Bayer A.G.), German Patent 1,910,895 (1970) [CA 73, 98,956w (1970)].

<sup>153</sup> W. Rohr, A. Fischer, and A. Zschocke (to BASF A.G.), German Patent 1,963,608 (1971) [CA 76, 3863p (1972)].

<sup>154</sup> A. D. Litt and J. Engelhart (to Esso Research & Engineering Co.), German Patent 2,123,312 (1971) [CA 76, 59,603w (1972)].

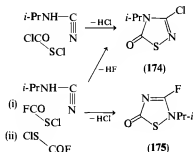
<sup>155</sup> J. Krenzer (to Velsicol Chemical Corp.), U.S. Patent 3,818,024 (1974) [CA 81, 120,641d (1974)].

<sup>156</sup> K. Findeisen, K. Wagner, and E. Klauke (to Bayer A.G.), German Patent 2,318,170 (1974) [CA 82, 125,981v (1975)].

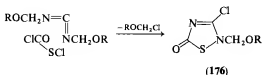
<sup>157</sup> A. H. Miller (to Esso Research & Engineering Co.), German Patent 2,119,782 (1971) [CA 76, 85,826r (1972)].

<sup>158</sup> H. J. Haase, German (East) Patent 77,493 (1970) [CA 75, 98,574 (1971)].

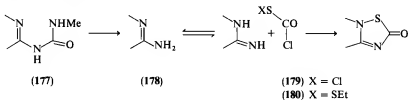
by side, involving, respectively, its SCl or COF group in the addition to the triple bond of the cyanamide.<sup>159</sup>



Condensation of bis(alkoxymethyl)carbodiimides and chlorothioformyl chloride in boiling benzene occurs with loss of one mole of alkoxymethyl chloride, and production of 2-alkoxymethyl-3-chloro- $\Delta^3$ -1,2,4-thiadiazolin-5-ones (176).<sup>160</sup>



Condensed ring systems incorporating 1,2,4-thiadiazole are formed when a heterocyclic compound (178) functioning as the amidine is condensed with chlorothioformyl chloride (179) or ethyldithiocarbonyl chloride (180): the scope of this synthesis is very wide indeed.



2-Aminothiazoles, for example, react with 179 in tetrahydrofuran to give tars, from which 2*H*-thiazolo[3,2-*b*]-1,2,4-thiadiazol-2-one (181) is isolable in 3% yield; the alternative use of 180 raises the yield to 25%.<sup>161,162</sup> The

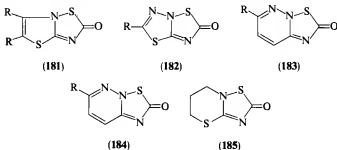
<sup>159</sup> A. Haas and V. Plass, *Chem. Ber.* **106**, 3391 (1973).

<sup>160</sup> P. Fischer (to Bayer A.G.), German Patent 1,925,995 (1970) [*CA* **74**, 31,757j (1971)].

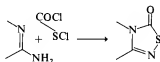
<sup>161</sup> K. Pilgram and R. D. Skiles, *J. Org. Chem.* **38**, 1575 (1973).

<sup>162</sup> K. H. Pilgram and R. D. Skiles (to Shell Oil Co.), U.S. Patent 3,726,891 (1973) [*CA* **78**, 159,615m (1973)].

method gives more favorable practical results when applied to the synthesis of the following condensed structures<sup>161</sup>: 6*H*-1,3,4-thiadiazolo[3,2-*b*]-1,2,4-thiadiazol-6-ones (**182**, 10–53%), 2*H*-1,2,4-thiadiazolo[2,3-*a*]pyridin-2-ones (**183**, 48%), 2*H*-1,2,4-thiadiazolo[2,3-*b*]pyridazin-2-ones (**184**), and 5,6-dihydro-2*H*-1,2,4-thiadiazolo[3,2-*b*]thiazin-2-one (**185**).<sup>161</sup>



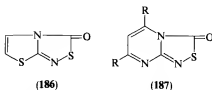
The interaction of comparable heterocyclic methylureas (**177**) and chlorothioformyl chloride (**179**) gives in some, but not all, cases identical results, due to initial loss of methyl isocyanate from **177**. Alternatively, the urea moiety may be preserved, when 2-hetaryl-1,2,4-thiadiazolidine-3,5-diones are formed, as described immediately above. The observations on record are too varied and extensive to be adequately summarized. A typical example of the reaction is the production of 2-(thiazol-2-yl)-4-methyl-1,2,4-thiadiazolidine-3,5-diones (**169**, Alk = Me, Ar = thiazol-2-yl).<sup>163</sup>



The addition of chlorothioformyl chloride to  $\alpha$ -amino-*N*-heterocycles can clearly take place in the opposite sense, the sulfur atom appearing adjacent to the exocyclic nitrogen of the starting material. This occurs when 2-aminothiazole or 2-amino- $\Delta^2$ -thiazoline react in ethanol-free chloroform, resulting in thiazolo[2,3-*c*]-1,2,4-thiadiazol-3-one (**186**) or its 5,6-dihydro analog. The structure of the latter has been confirmed by X-ray analysis. 2-Amino- (and 4-amino-2,6-dimethyl)pyrimidine similarly afford 1,2,4-thiadiazolo[4,3-*a*]pyrimidin-3-one (**187**, R = H, 34%) and 5,7-dimethyl-1,2,4-thiadiazolo[4,3-*c*]pyrimidin-3-one (39%), respectively. Possible mechanisms of the reactions have been discussed.<sup>164</sup>

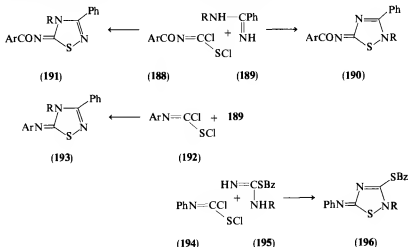
<sup>163</sup> K. Pilgram and R. D. Skiles, *J. Org. Chem.* **38**, 1578 (1973).

<sup>164</sup> D. Baldwin and P. van den Broek, *J. C. S. Perkin I*, 375 (1975).



b. *N*-Substituted *S*-Chloroisoithiocarbamoyl Chlorides, ( $RN=$ )-CClSCl. *N*-Substituted *S*-chloroisoithiocarbamoyl chlorides are accessible by the controlled chlorination of isothiocyanate esters.<sup>165</sup> They are comparable with chlorothioformyl chloride both formally, and in their behavior, but their nitrogen function confers an additional variable on the versatility of these reagents (see *c* of this Section).

The condensation of *N*-acyl-*S*-chloroisoithiocarbamoyl chlorides (**188**) and amidines (**189**) yields 5-benzoylimino-3-phenyl-2-aryl- $\Delta^3$ -1,2,4-thiadiazolines (**190**) as major, and the isomeric  $\Delta^2$ -1,2,4-thiadiazolines (**191**) as minor products. Analogs (**193**) of the latter are formed exclusively from *N*-aryl-*S*-chloroisoithiocarbamoyl chlorides (**192**). The divergent course of the reaction is ascribed to the different reactivity of the chlorine atoms in the two reagents (**188**, **192**). It is plausible that the initial nucleophilic attack of the base occurs at the imido carbon of **188**, but at the sulfenyl sulfur of **192**.<sup>166</sup> The condensation of *N*-phenyl-*S*-chloroisoithiocarbamoyl chloride (**194**) and isothioureas (**195**) similarly yields the 1,2,4-thiadiazolines (**196**).<sup>167</sup>



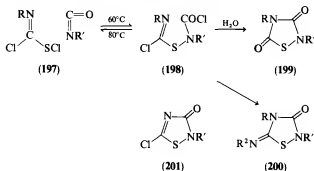
<sup>165</sup> G. Ottmann and H. Hooks, *Angew. Chem., Int. Ed. Engl.* **4**, 432 (1965); *J. Org. Chem.* **31**, 838 (1966).

<sup>166</sup> R. Neidlein and H. Reuter, *Tetrahedron* **27**, 4117 (1971).

<sup>167</sup> A. S. Mahajan, P. A. Ganeshpure, and M. G. Paranjpe, *J. Indian Chem. Soc.* **53**, 89 (1976).

c. *S*-(*N*-Chlorocarbonylamino)isothiocarbamoyl Chlorides. In addition to the foregoing reactions, *N*-substituted *S*-chloroisothiocarbamoyl chlorides may participate in an entirely different 1,2,4-thiadiazole synthesis, in which it is their sulfur and nitrogenous centers that are involved in the cyclization. This synthetic route, though of Type A, has been deferred to this Section, so that all the reactions of these reagents may appear together.

*N*-Substituted *S*-chloroisothiocarbamoyl chlorides (**197**) react additively with isocyanates to form the highly reactive *S*-(*N*-chlorocarbonylamino)-isothiocarbamoyl chlorides (**198**) nearly quantitatively. These are cyclized to the 3,5-diones (**199**) by water or aqueous alcohol in a vigorous exothermic reaction, with evolution of hydrogen chloride.<sup>168,169</sup> Aminolysis of **198** produces 5-imino-1,2,4-thiadiazolidin-3-ones (**200**).<sup>170</sup>



The reaction may be performed in one step by passing chlorine into a solution of the isothiocyanate and isocyanate in carbon tetrachloride, and precipitating the intermediate **198** with ether; hydrolysis completes the process.<sup>171,172</sup> Under appropriate conditions, it may be terminated at an earlier stage, and 2-substituted 5-chloro-1,2,4-thiadiazolin-3-ones (**201**) isolated.<sup>173</sup> This has been done in the condensation of **202** and trimethyl-

<sup>168</sup> G. Ottmann and H. Hooks, *Angew. Chem., Int. Ed. Engl.* **5**, 672 (1966); (to Olin Corp.), U.S. Patent 3,282,950 (1966) [*CA* **66**, 10,939r (1967)]; U.S. Patent 3,374,240 (1968) [*CA* **69**, 52,146w (1968)].

<sup>169</sup> J. Krenzer (to Velsicol Chemical Corp.), U.S. Patent 3,900,485 (1975) [*CA* **84**, 44,069t (1976)].

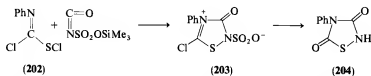
<sup>170</sup> G. Ottmann and H. Hooks, *J. Heterocycl. Chem.* **4**, 365 (1967).

<sup>171</sup> W. Rohr and A. Fischer (to BASF A.G.), German Patent 2,109,755 (1972) [*CA* **77**, 164,674p (1972)].

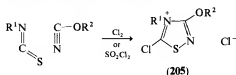
<sup>172</sup> W. Rohr, A. Fischer, and A. Zschocke (to BASF A.G.), U.S. Patent 3,711,492 (1973) [*CA* **78**, 84,420h (1973)].

<sup>173</sup> G. Zumach, H. Holschmidt, and E. Kuehle (to Bayer A.G.), German Patent 1,907,116 (1970) [*CA* **73**, 98,957x (1970)].

silyloxysulfonyl isocyanate in inert solvents: the intermediates **203** yield the 4-substituted 1,2,4-thiadiazolidine-3,5-diones (**204**) on hydrolysis.<sup>174</sup>

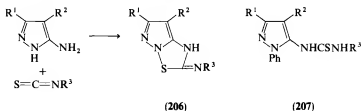


The condensation of cyanate esters with the reagents (generated from isothiocyanates *in situ*) produces 4-substituted 3-alkoxy-5-chloro-1,2,4-thiadiazolium chlorides (**205**) in one stage.<sup>175</sup>



### 5. Syntheses from Amidines and Isothiocyanate Esters

The interaction of 1,3- or 1,4-diphenyl-5-aminopyrazole with isothiocyanate esters gives the expected thioureas (**207**). 5-Aminopyrazoles unsubstituted at N1, however, undergo simultaneous cyclization to 6*H*,7*H*-pyrazolo[3,2-*b*]-1,2,4-thiadiazoles (**206**).<sup>176</sup>



In the production of 2-isothiocyanatopyridine (**208**) from 2-aminopyridine and thiophosgene,<sup>177</sup> continued reaction yields 2*H*-1,2,4-thiadiazolo[2,3-*a*]-pyridine-2-thione (**209**, 48%) by a mechanism so far not elucidated.<sup>178</sup>

<sup>174</sup> Farbenfabriken Bayer A.G., French Patent 2,002,569 (1969) [CA 72, 111,478i (1970)].

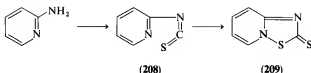
<sup>175</sup> G. Zumach, H. Holtschmidt, and E. Kuehle (to Bayer A.G.), British Patent 1,196,197 (1970) [CA 74, 3635z (1971)].

<sup>176</sup> W. Dymek and Z. Ryznerski, *Acta Pol. Pharm.* **25**, 375 (1968).

<sup>177</sup> O. E. Schultz and K. K. Gauri, *Arch. Pharm. (Weinheim, Ger.)* **295**, 146 (1962).

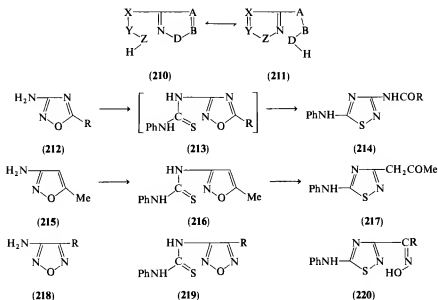
<sup>178</sup> W. Stadlbauer, T. Kappe, and E. Ziegler, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **33B**, 89 (1978).





### 6. Syntheses from 1,2,4-Oxadiazoles, etc.

The interaction of 5-substituted 3-amino-1,2,4-oxadiazoles (212) with phenyl isothiocyanate produces 3-acylamino-5-amino-1,2,4-thiadiazoles (214) in one stage, evidently by the rearrangement of the intermediate thioureides (213).<sup>179</sup> The isoxazoles (215) and 1,2,5-oxadiazoles (218) react analogously, but with decreasing tendency to rearrangement. Thus, in contrast to 213, the intermediate thiourea (216) is isolable, while 219 is actually the final product, and requires alkaline conditions for its separate rearrangement. The action of potassium hydroxide yields, according to the conditions, the E or Z forms of 3-acetyl-5-anilino-1,2,4-thiadiazole oxime (220), the configurations of which were determined by the results of their Beckmann rearrangements.<sup>180</sup> The reactions are examples of a group of heterocyclic rearrangements of the general type (210  $\rightarrow$  211): they were claimed to be the first cases in which sulfur forms part of the X—Y—Z system.<sup>179</sup>



<sup>179</sup> M. Ruccia, N. Vivona, and G. Cusmano, *J. C. S. Chem. Commun.*, 358 (1974).

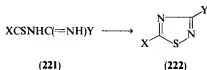
<sup>180</sup> N. Vivona, G. Cusmano, and G. Macaluso, *J. C. S. Perkin I*, 1616 (1977).

## C. TYPE C SYNTHESSES

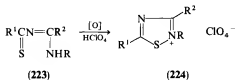


## 1. Oxidation of Amidinothiono Compounds

The versatile and facile synthesis of 1,2,4-thiadiazoles by the oxidative cyclization of compounds incorporating an amidinothiono group<sup>3</sup> continues to be widely used, partly because of the ready accessibility of many of the linear starting materials (**221**). The groupings flanking the amidinothiono core determine the nature of the 3- and 5-substituents of the resulting heterocycles; the numerous examples are classified as far as possible, from this point of view.



a. *Thioacylamidines* ( $\text{R}^1\text{CSNHC(=NH)R}^2$ ). The conversion of thioacylamidines to 3,5-dialkyl(or aryl)-1,2,4-thiadiazoles (**221**  $\rightarrow$  **222**; X, Y = Alk or Ar)<sup>3</sup> is the simplest representative of this synthesis. One of the two hydrogen atoms required for the oxidative ring closure may be supplied by protonation: thus treatment of **223** with hydrogen peroxide in the presence of perchloric acid yields 2-alkyl-3,5-diaryl-1,2,4-thiadiazolium perchlorates (**224**;  $\text{R}^1, \text{R}^2 = \text{Ar}$ ,  $\text{R} = \text{Alk}$ ).<sup>181</sup>

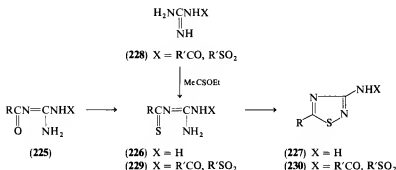


b. *Thioacylguanidines* [ $\text{RCSNHC(=NH)NHX}$ ]. The oxidation of thioacylguanidines (**226**) prepared *in situ* from acylguanidines (**225**) and phosphorus pentasulfide in pyridine, produces 5-substituted 3-amino-1,2,4-thiadiazoles (**227**) in moderate yield. The intermediates (**226**) appear to be somewhat labile.<sup>182</sup> Similarly, 1-acyl(or sulfonyl)-3-thioacylguanidines (**229**),

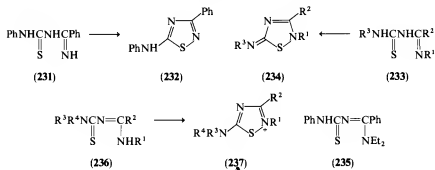
<sup>181</sup> J. Liebscher, German (East) Patent 136,965 (1979) [CA **92**, 58,789e (1980)].

<sup>182</sup> J. Goerdeler and P. Mertens, *Chem. Ber.* **103**, 1805 (1970).

obtained from acylguanidines (**228**) and thioacid-*O*-ester in the presence of sodium hydride, furnish the appropriate 3-acylamido analogs (**230**).<sup>183</sup>



c. *Imidothiureas* ( $\text{XNHCSNHC}(=\text{NH})\text{R}$ ). In an attempted thiazole synthesis involving treatment of the imidothiurea **231** with bromonitromethane, the thiadiazole **232** was formed as the main product by direct oxidative cyclization. In the case of the more highly substituted homologs (**235**), this reaction is suppressed.<sup>184</sup> Imidothiureas of type **233** are ring-closed to 2,3-disubstituted 5-imino- $\Delta^3$ -1,2,4-thiadiazolines (**234**).<sup>185</sup> As in the case of the thioacylamidines (see a, above), the more highly substituted imidothiureas (**236**) may be oxidized to **237** in the presence of perchloric acid, protonation providing one of the centers for the cyclization.<sup>186</sup>



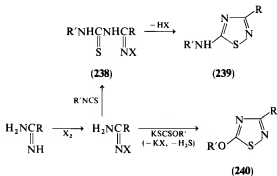
<sup>183</sup> B. Junge, *Justus Liebigs Ann. Chem.*, 1961 (1975); (to Bayer A.G.), German Patent 2,402,228 (1975) [*CA* **83**, 179,073q (1975)].

<sup>184</sup> S. Rajappa and B. G. Advani, *Indian J. Chem. Sect. B* **16B**, 749 (1978).

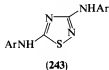
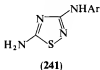
<sup>185</sup> G. Barnikow and H. Ebeling, *Z. Chem.* **12**, 130 (1972).

<sup>186</sup> J. Liebscher, J. Arnold, and H. Hartmann, German (East) Patent 131,373 (1978) [*CA* **90**, 87,470h (1979)].

In a variation of this synthesis, the amidine is N-halogenated prior to its condensation with an isothiocyanate ester: the resulting *N*-haloimidothioureas (**238**) are readily cyclized to **239** by alkalis. By employing bromine in conjunction with methylene chloride–aqueous alkali as the reaction medium, the reaction may be performed in one operation. 3-Trichloromethyl-5-(substituted)amino-1,2,4-thiadiazoles have been produced by this method.<sup>187</sup> The use of potassium ethyl xanthate similarly yields the 5-ethoxy analogs (**240**; e.g., R = CCl<sub>3</sub>, R<sup>1</sup> = Et) directly, with elimination of the elements of hydrogen sulfide.<sup>188</sup>



d. *Amidinothiourea* (XNHCSNHC(=NH)NHY). The oxidative cyclization of amidinothioureas, probably the most frequently used variation of this synthesis,<sup>3</sup> provides 3,5-diamino-1,2,4-thiadiazoles of various degrees of substitution. The appropriate amidinothioureas have generally been prepared by conventional methods,<sup>3</sup> or more recently by the condensation of (substituted) thioureas with cyanamides or carbodiimides (see Section

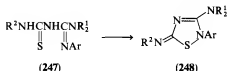


<sup>187</sup> J. H. Tobin (to Olin Corp.), U.S. Patent 4,107,377 (1978) [CA 90, 87,442a (1979)].

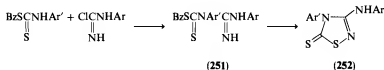
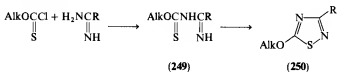
<sup>188</sup> E. F. Rothgery and H. J. Schroeder (to Olin Corp.), U.S. Patent 4,143,044 (1979) [CA 90, 186,962 (1979)].

II,A,2,d), and are readily cyclizable by the action of bromine or hydrogen peroxide. In this way, 1,2,4-thiadiazole derivatives of types **241**,<sup>189</sup> **242**,<sup>56</sup> **243**,<sup>190</sup> **244**,<sup>41</sup> **245**,<sup>57</sup> and **246**,<sup>54</sup> have been produced, but other variants are possible.

Trisubstituted amidinothioureas of type **247**, obtainable from formamido-*o*-alkyl isothiocyanates [ $R^1_2NC(=NAr)NCS$ ], are cyclized to **248**,<sup>98,191</sup> which are isolated advantageously as salts (hydrobromides, hydriodides); with suitable precautions, the somewhat labile bases are isolable.<sup>98</sup>



*e. Thio- and Dithiocarbamate Derivatives.* Imidoylthiocarbamate esters (**249**), readily accessible by the condensation of amidines and *O*-alkyl chlorothiocarbonates, are ring-closed to 3-substituted 5-alkoxy-1,2,4-thiadiazoles (**250**) upon oxidation. 5-Ethoxy-3-trichloromethyl-1,2,4-thiadiazole (**250**,  $R = CCl_3$ ,  $Alk = Et$ ) and its homologs are produced in high yields by this route.<sup>192</sup>



The cyclization of amidinodithiocarbamate esters similarly leads to 5-mercapto-1,2,4-thiadiazoles. Thus, *S*-benzylphenylamidinophenylthio-

<sup>189</sup> L. Azhakumoni, C. P. Joshua, and K. N. Rajasekharan, *Indian J. Chem., Sect. B* **15B** 490 (1977).

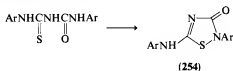
<sup>190</sup> M. S. Chande, *Indian J. Chem.* **8**, 137 (1970).

<sup>191</sup> W. Abraham and G. Barnikow, *Tetrahedron* **29**, 699 (1973).

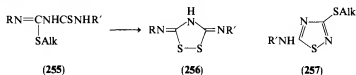
<sup>192</sup> Olin Mathieson Chemical Corp., Netherlands Patent Appl. 6,610,627 (1967) [*CA* **68**, 29,701u (1968)].

carbamate (**251**,  $\text{Ar}, \text{Ar}^1 = \text{Ph}$ , synthesized as shown) is simultaneously debenzylated<sup>193</sup> and ring-closed on treatment with bromine in chloroform, yielding 3-anilino-4-phenyl- $\Delta^2$ -thiadiazoline-5-thione (**252**). The properties of the product, including the resemblance of its IR spectrum and that of Hector's base, appear to exclude its possible alternative formulation as **253**.<sup>194</sup>

f. *Thiobiurets and Dithiobiurets.* The well-established conversion of thiobiurets to 5-amino-3-oxy-1,2,4-thiadiazoles<sup>3</sup> has been further illustrated.<sup>195</sup> The oxidative cyclization of 1,5-diphenyl-2-thiobiuret is of some interest, in that the resulting 5-anilino-2-phenyl- $\Delta^4$ -1,2,4-thiadiazolin-3-one (**254**) is nonidentical (mp 232°C, alkali soluble) with Dost's keto compound obtained on treatment of Hector's base with hydrochloric acid.<sup>32</sup>



The oxidation of 2-S-allyl-1,5-diaryl-2,4-dithiobiurets (**255**,  $\text{R} = \text{R}^1 = \text{Ar}$ ) by iodine in boiling chloroform proceeds chiefly with simultaneous dealkylation<sup>193</sup> to yield 3,5-diarylimino-1,2,4-dithiazolidines (**256**).<sup>196</sup> The 5-mono-aryl analogs (**255**,  $\text{R}^1 = \text{Ph}$ ,  $\text{R} = \text{H}$ ) react analogously, but also produce the 1,2,4-thiadiazoles (**257**) as minor by-products.<sup>197</sup>



g. *Condensed 1,2,4-Thiadiazoles.* When the amidinothiono grouping forms part of a heteroring, its oxidative cyclization produces 1,2,4-thiadiazoles that are incorporated into fused ring systems. The scope of this approach is clearly very wide, and has been illustrated using a number of heterocyclic patterns. As in the case of the linear analogues, the synthesis may be subdivided into reactions of structures bearing thioamido, thioureido, or dithiocarbamido groups adjacent to a ring nitrogen.

<sup>193</sup> V. K. Verma, *J. Sci. Ind. Res., Sect. B* **21**, 491 (1962); *Indian J. Chem.* **1**, 116 (1963).

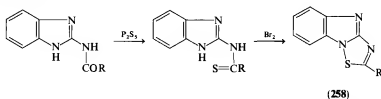
<sup>194</sup> M. G. Paranjpe, *J. Indian Chem. Soc.* **43**, 45 (1966).

<sup>195</sup> M. N. Basyouni and A. M. A. El-Khamry, *Chem. Ind. (London)*, 670 (1978).

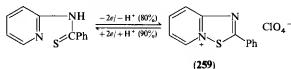
<sup>196</sup> R. Singh, V. K. Verma, and C. V. Agarwal, *J. Indian Chem. Soc.* **52**, 444 (1975), and preceding papers.

<sup>197</sup> R. Singh and V. K. Verma, *Indian J. Chem., Sect. B* **15B**, 192 (1977).

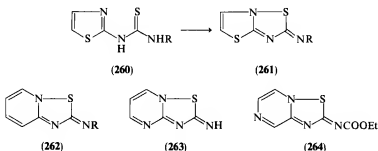
Thus, a variety of thioamides derived from 2-aminobenzimidazole are oxidized by bromine to 2-substituted 1,2,4-thiadiazolo[2,3-*a*]benzimidazoles (**258**).<sup>198</sup>



The cyclization may be performed by anodic oxidation: cyclodehydration of 2-thioamidopyridine to 2-phenyl-1,2,4-thiadiazolo[2,3-*a*]pyridinium perchlorate (**259**) occurs in excellent yield at a graphite anode. The process is reversed by the corresponding reduction at a platinum cathode.<sup>199</sup>



The action of bromine in chloroform on appropriate heterocyclic thioureas (e.g., **260**) affords high yields of iminoderivatives of the corresponding condensed structures, including 1,2,4-thiadiazolo[3,2-*b*]thiazole (**261**, R = H),<sup>200</sup> 1,2,4-thiadiazolo[2,3-*a*]pyridine (**262**, R = H),<sup>200,201</sup> and 1,2,4-thiadiazolo[2,3-*a*]pyrimidine (**263**).<sup>200</sup>



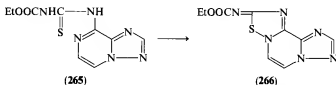
<sup>198</sup> C. C. Beard (to Syntex Inc.), German Patent 2,446,119 (1975) [CA 83, 28,234s (1975)]; U.S. Patents 3,946,031, 3,976,654 (1976), 4,009,164 (1977) [CA 85, 21,381v (1976); 86, 5464q, 189,943z (1977)].

<sup>199</sup> I. Tabakovic, M. Trkovnik, M. Batusic, and K. Tabakovic, *Synthesis*, 590 (1979).

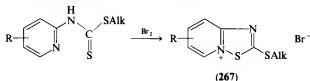
<sup>200</sup> G. Barnikow and J. Boedeker, *J. Prakt. Chem.* 313, 1148 (1971).

<sup>201</sup> R. L. N. Harris, *Aust. J. Chem.* 25, 993 (1972).

1-Ethoxycarbonyl-3-heterylthiureas similarly give rise to the corresponding carboximino derivatives of the following: **261** ( $R = \text{COOEt}$ ),<sup>202</sup> **262** ( $R = \text{COOEt}$ ),<sup>203-205</sup> 1,2,4-thiadiazolo[2,3-*b*]pyridazine,<sup>203</sup> 1,2,4-thiadiazolo[2,3-*a*]pyrazine (**264**),<sup>203</sup> 1,2,4-thiadiazolo[2,3-*c*]pyrimidine,<sup>206</sup> and 1,2,4-thiadiazolo[2,3-*b*]indazole.<sup>206</sup> The tricyclic ring system (**266**, 2*H*-1,2,4-thiadiazolo[2,3-*a*]-1,2,4-triazolo[5,1-*c*]pyrazine) is obtainable from **265**.<sup>204</sup>



In the third reported variation of this synthesis, oxidative cyclization of *N*-(2-pyridyl)-*S*-alkyldithiocarbamates by bromine in glacial acetic acid yields 2-alkylthiopyrido[1,2-*b*]-1,2,4-thiadiazolium bromides (**267**).<sup>207</sup>



## 2. Synthesis from Dithiazoles

One group of conversions of 1,2,4-dithiazoles to 1,2,4-thiadiazoles involving [3 + 2] cycloadditions is described among the syntheses of type A (see Section II.A.5). It remains to deal with those reactions that may be classified appropriately as ring closures of type C.

a. “*Isoperthiocyanic Acid*” and *Homologs*. The nature of “isoperthiocyanic” and “perthiocyanic” acid, and the perplexing question of their relationship to one another,<sup>1,2</sup> have been fully elucidated only recently as

<sup>202</sup> M. Nagano, M. Oshige, T. Kinoshita, T. Matsui, J. Tobitsuka, and K. Oyamada, *Chem. Pharm. Bull.* **21**, 2408 (1973).

<sup>203</sup> B. Koren, B. Stanovnik, and M. Tisler, *Org. Prep. Proced. Int.* **7**, 55 (1975).

<sup>204</sup> B. Vercek, B. Stanovnik, and M. Tisler, *Heterocycles* **11**, 313 (1978).

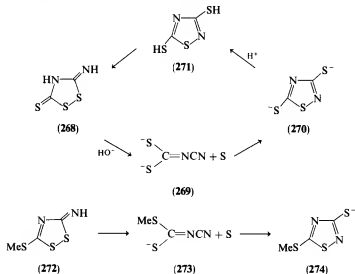
<sup>205</sup> For an X-ray analysis of this ring-system, see I. Leban, *Acta Crystallogr., Sect. B* **B32**, 1601 (1976).

<sup>206</sup> B. Koren, B. Stanovnik, and M. Tisler, *J. Heterocycl. Chem.* **14**, 621 (1977).

<sup>207</sup> R. L. N. Harris and R. Spaun (to Ciba Geigy A.G.), German Patent 2,258,279 (1973) [*CA* **79**, 92,236p (1973)].



interconversions between dithiazoles and thiadiazoles.<sup>3,208</sup> It is now established that the interaction of hydrochloric acid and ammonium thiocyanate gives 3-imino-5-thiono-1,2,4-dithiazolidine (isoperthiocyanic acid, **268**), which isomerizes under the influence of alkali, with intermediate formation of cyanodithioimidocarbonate (**269**) and transient liberation of sulfur) to the "perthiocyanate" anion (**270**). Acidification of **270** liberates the unstable perthiocyanic acid (3,5-dimercapto-1,2,4-thiadiazole, **271**) which reverts spontaneously to the starting material (**268**).<sup>3,208</sup> The dipotassium salt of 3,5-dimercapto-1,2,4-thiadiazole (**270**) is in fact most conveniently produced by refluxing a solution of dipotassium cyanodithioimidocarbonate (**269**, for preparation, see below) with sulfur in methanol.<sup>209</sup> The action of alkali on the 5-methylthio homolog (**272**)<sup>210</sup> of **268** similarly yields the salt of *S*-methyl cyanodithioimidocarbonate (**273**) as the main product (84%), together with a little of the 5-methylthio heterocycle (**274**, 7%); these were not isolated, however, but were identified gas-chromatographically, and by their further methylation *in situ*.<sup>211</sup>



b. *Other Reactions.* The alkylation of "phenylthiurets" (**275**, 3,5-diimino-1,2,4-dithiazolidines) is attended by isomerization of the dithiazole to the thiadiazole ring system, presumably under the influence of the alkaline

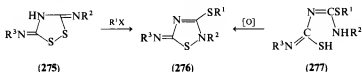
<sup>208</sup> J. Goerdeler and G. Sperling, *Chem. Ber.* **90**, 892 (1952).

<sup>209</sup> W. A. Thaler and J. R. McDivitt, *J. Org. Chem.* **36**, 14 (1971).

<sup>210</sup> R. E. Allen, R. S. Shelton, and M. G. Van Campen, *J. Am. Chem. Soc.* **76**, 1158 (1954).

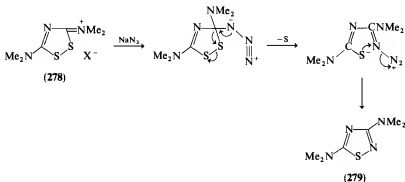
<sup>211</sup> R. Seltzer, *J. Org. Chem.* **34**, 2562 (1969).

media. Thus, methylation or benzylation (of **275**) in alkali gives 5-imino-3-alkylthio-2-phenyl- $\Delta^3$ -1,2,4-thiadiazolines (**276**,  $R^1 = \text{Me}, \text{CH}_2\text{Ph}$ ;  $R^2 = \text{Ph}$ ,  $R^3 = \text{H}$ ). Their structure is confirmed by their alternative synthesis by the oxidative cyclization of 2-S-alkyliso-1-phenyldithiobiurets (**277**). Conversely, the dealkylation by concentrated hydrochloric acid, of the 1,2,4-thiadiazoline **276** ( $R^1 = t\text{-Bu}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{Ph}$ , obtained from **277**) proceeds with opposite isomerization, yielding **275** ( $R^2 = \text{H}$ ,  $R^3 = \text{Ph}$ ). Possible mechanisms of these reactions were considered, but the issue is complicated by the fact that different structural types of the 1,2,4-thiadiazole system appear to arise under the action of different alkyl halides.<sup>212</sup>



3,5-Bis(dimethylamino)-1,2,4-dithiazolium chloride (**278**) reacts with sodium azide in dimethylformamide, yielding the correspondingly substituted 1,2,4-thiadiazole (**279**, 75%), possibly by the mechanism shown. Reactants (**278**) bearing nonidentical substituents may yield pairs of isomeric 1,2,4-thiadiazoles, but usually produce only the one arising by attack of the azide at the heterocarbon bearing the less highly substituted amino group.<sup>213</sup> The action of potassium cyanate in this reaction yields the expected 4,6-bis(dialkylamino)-2*H*-1,3,5-thiadiazin-2-ones, but 1,2,4-thiadiazoles arise in anomalous cases, with elimination of carbon monoxide.<sup>214</sup>

The chemistry of the *isothiocyanate oxides* and *sulfides* for which 1,2,4-thiadiazole structures have been considered at various times<sup>3</sup> (see especially



<sup>212</sup> G. Bhaskaraiah, *Indian J. Chem.*, **12**, 134 (1974).

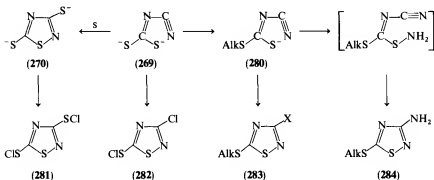
<sup>213</sup> J. E. Oliver, *J. Org. Chem.*, **36**, 3465 (1971).

<sup>214</sup> J. E. Oliver, B. A. Bierl, and J. M. Ruth, *J. Org. Chem.*, **37**, 131 (1972).

Ref. 1), are now known to belong almost entirely to the domain of the 1,2,4-dithiazoles, except where isomerization to the alternative ring system occurs.<sup>3</sup> The results of some recent work,<sup>215-217</sup> including those of spectral studies,<sup>218</sup> are in accord with these conclusions.<sup>3</sup> (see also Section II.C,3).

c. *From Cyanodithioimidocarbonates.* Dipotassium cyanodithioimidocarbonate (**269**) and its *S*-alkyl homologs (**280**) function as the intermediates in interconversions between 1,2,4-dithiazoles and 1,2,4-thiadiazoles, but are also accessible by other methods and serve as starting materials in some additional thiadiazole syntheses. Because of the close relationship of these reactions to those described in the foregoing Section, they are expediently included at this point.

Dipotassium cyanodithioimidocarbonate (**269**) is readily produced from cyanamide and carbon disulfide in alkali, and affords the *S*-alkyl derivatives (**280**) in good yield upon treatment with a variety of primary and secondary alkyl halides.<sup>219,220</sup> The action of chlorine converts the parent salt (**269**) to 3-chloro-1,2,4-thiadiazole-5-sulfonyl chloride (**282**, 85–100%), and the bromo analog is similarly accessible.<sup>209,221,222</sup> Dipotassium perthiocyanate (**270**, obtained from **269** and sulfur<sup>209</sup>) is chlorinated to the stable bisulfenyl



<sup>215</sup> M. G. Paranjpe, *Indian J. Chem.*, **6**, 132 (1968).

<sup>216</sup> E. Eghtessad and G. Zinner, *Arch. Pharm. (Weinheim, Ger.)* **312**, 1027 (1979).

<sup>217</sup> G. Zinner and E. Eghtessad, *Dtsch. Apoth.-Ztg.* **119**, 203 (1979).

<sup>218</sup> M. G. Paranjpe and R. K. Gosair, *Indian J. Chem.*, **5**, 125 (1967).

<sup>219</sup> R. J. Timmons and L. S. Wittenbrook, *J. Org. Chem.*, **32**, 1566 (1967); L. S. Wittenbrook, G. L. Smith, and R. J. Timmons, *ibid.*, **38**, 465 (1973).

<sup>220</sup> R. J. Timmons and L. S. Wittenbrook (to O. M. Scott & Sons), U.S. Patents 3,658,901 (1972); 3,736,328 (1973); 3,825,551 (1974) [*CA* **77**, 87,904j (1972); **79**, 42,517k (1973); **81**, 136,134b (1974)].

<sup>221</sup> R. Neidlein and H. Reuter, *Arch. Pharm. (Weinheim, Ger.)* **305**, 373 (1972).

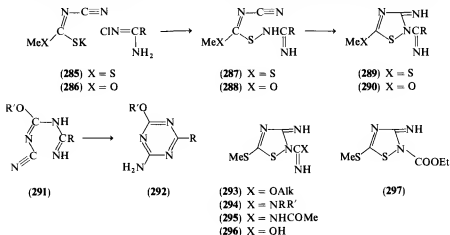
<sup>222</sup> W. A. Thaler (to Esso Research & Engineering Co.), U.S. Patent 3,691,183 (1972) [*CA* **77**, 152,191r (1972)].

chloride (**281**).<sup>209,221</sup> The parallel oxidative cyclization of *S*-alkylcyanodithioimidocarbonates (**280**) by sulfuryl chloride or bromine yields 5-alkylthio-3-halogeno-1,2,4-thiadiazoles (**283**).<sup>219,220</sup>

Finally, in order to confine the reactions of the cyanodithioimidocarbonates (**280**) to one Section, their participation in a synthesis of type E is now included: the reaction concerned is their condensation with *N*-chloroamino compounds. Potassium *S*-alkylcyanodithioimidocarbonates (**280**) react with chloramine itself (produced *in situ* from aqueous ammonia and chlorine) to afford good yields of 3-amino-5-alkylthio-1,2,4-thiadiazoles (**284**).<sup>223,224</sup>

Similarly, the condensation of **285** with *N*-chloroamidines in chloroform or acetonitrile readily yields 2-imidoyl-3-imino-5-methylthio- $\Delta^4$ -1,2,4-thiadiazolines (**289**) in one stage.<sup>225,226</sup> The intermediate formation of the linear precursors (**287**) is indicated by the isolation, and separate cyclization (to **290**) of their oxygen analogs (**288**) in the corresponding condensations involving potassium alkoxythiocarbonylcyanamides (**286**). Here, the formation of the substituted triazines **292** via **291** (arising from **286** by a desulfurization mechanism) occurs as a side reaction in certain solvents, but becomes the exclusive reaction in acetonitrile.<sup>225</sup>

The synthesis may clearly be varied in obvious ways, and yields, on employing **285** in conjunction with the *N*-chloro derivatives of *O*-alkylisoureas,



<sup>223</sup> W. Walek, M. Pallas, and M. Augustin, *Tetrahedron* **32**, 623 (1976).

<sup>224</sup> M. Augustin, K. Goetzschel, M. Pallas, and W. Walek, German (East) Patent 119,791 (1976) [*CA* **86**, 106,601n (1977)].

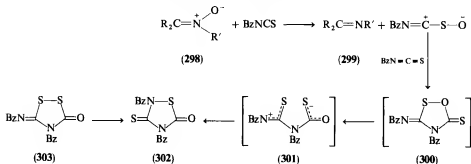
<sup>225</sup> T. Fuchigami and K. Odo, *Bull. Chem. Soc. Jpn.* **49**, 3165 (1976); *Chem. Lett.* 917 (1973).

<sup>226</sup> K. Odo (to Sanwa Chemical Co.), Japanese Patent 75/95,270 (1975) [*CA* **84**, 105,601j (1976)].

guanidines, or guanyurethane, the appropriate substituted  $\Delta^4$ -1,2,4-thiadiazolines (**293**, **294**, **295**). 2-Methoxyimido-3-imino-5-methylthio- $\Delta^4$ -1,2,4-thiadiazoline (**293**) thus obtained is convertible to the urea (**296**) by acid hydrolysis, and to the amidino derivatives (**294**) by aminolysis.<sup>227</sup> A comparable group of reactions, starting with potassium alkoxythiocarbonylcyanamides (**286**) affords the 5-alkoxy analogs of **293**, **294**, and **296**.<sup>228</sup> In yet another variation, the condensation of **285** and *N*-chlorocarbamates (CINHCOOEt) results in the 2-alkoxycarbonyl derivatives (**297**).<sup>229</sup>

### 3. Oxidation of Isothiocyanates

The interaction of isothiocyanate esters and nitrones<sup>230</sup> (**298**) (intended as a synthesis of 1,2,4-oxadiazolidine-5-thiones by [3 + 2] cycloaddition) unexpectedly gave the 2,4-disubstituted 1,2,4-thiadiazolidine-5-oxo-3-thione (**302**) (i.e., a product formerly referred to as an isothiocyanate oxide<sup>3</sup>). Its formation was accounted for by the initial transfer of oxygen to the isothiocyanate, (the remaining azomethine **299** being isolable), followed by the condensation and rearrangement steps (**300** → **301** → **302**) shown. Its alternative synthesis by isomerization of the 1,2,4-dithiazolium salt (**303**) supported the assigned structure and its proposed mode of formation.<sup>216,217</sup>



### 4. Synthesis from Imino-1,3-thiazetidines

2-Imino-1,3-thiazetidines (**304**, accessible from 1,3-disubstituted thioureas and diiodomethane<sup>231</sup>) are oxidized by hydrogen peroxide to yield 3-oxo-

<sup>227</sup> T. Fuchigami and K. Odo, *Bull. Chem. Soc. Jpn.* **48**, 310 (1975).

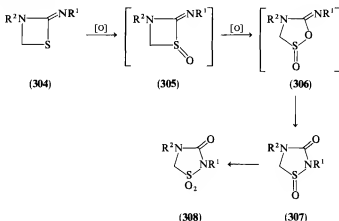
<sup>228</sup> T. Fuchigami, T. Nonaka, and K. Odo, *Bull. Chem. Soc. Jpn.* **49**, 3170 (1976).

<sup>229</sup> T. Fuchigami and T. Nonaka, *Chem. Lett.* 829 (1979).

<sup>230</sup> J. Hamer and A. Macaluso, *Chem. Rev.* **64**, 473 (1964); G. R. Delpierre and M. Lamchen, *Rev., Chem. Soc.* **19**, 329 (1965).

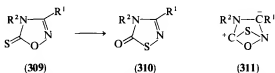
<sup>231</sup> W. Ried, W. Merkel, and O. Moesinger, *Justus Liebigs Ann. Chem.*, 1362 (1973).

1,2,4-thiadiazolidine 1-oxides (307), with simultaneous ring expansion.<sup>232</sup> Their structure was established by X-ray analyses of the 2-methyl(and benzyl)-4-phenyl derivatives.<sup>233</sup> Further oxidation produces the 1,1-dioxides (308). The reaction is visualized to involve insertion of oxygen into the primary S-oxide (305  $\rightarrow$  306) in the manner of the Baeyer–Villiger oxidation; subsequent Dimroth rearrangement of the oxathiazolidine (306) results in the final products (307).<sup>232</sup> The classification of this route as a synthesis of type C, though somewhat arguable, is based on the nature of this final cyclization stage.



### 5. Synthesis from 1,2,4-Oxadiazoles

3,4-Disubstituted  $\Delta^2$ -1,2,4-oxadiazoline-5-thiones (309), though generally stable compounds, undergo thermal rearrangement to the  $\Delta^2$ -1,2,4-thiadiazolin-5-ones (310). In some examples (e.g.,  $R^1 = \text{Ph}$ ,  $R^2 = \text{Me}$ , Et, Ph), reaction proceeds slowly in diphenyl ether at 200°C. More generally, the rearrangement occurs under the catalytic influence of copper powder, or upon photolysis, in the latter case possibly by way of intermediates of type 311.<sup>234</sup>



<sup>232</sup> W. Ried, O. Moesinger, and W. Schuckmann, *Angew. Chem., Int. Ed. Engl.* **15**, 103 (1976).

<sup>233</sup> W. Schuckmann, H. Fuess, O. Moesinger, and W. Ried, *Acta Crystallogr., Sect. B* **B34**, 1516 (1978).

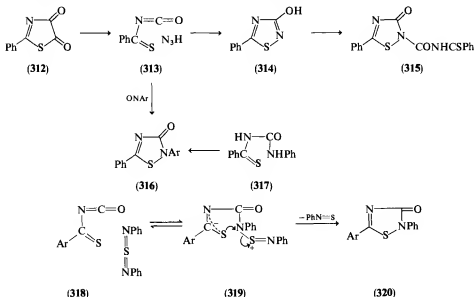
<sup>234</sup> A. Pelter and D. Sumengen, *Tetrahedron Lett.*, 1945 (1977).

## D. TYPE E SYNTHESSES



## 1. Syntheses from Thiobenzoyl Isothiocyanate

Thiobenzoyl isocyanate (**313**) may contribute four of the atoms (S—C—N—C) of the 1,2,4-thiadiazole ring system, the fifth being provided by a suitable nitrogenous compound. The reactant (**313**) is readily generated *in situ* from 2-phenylthiazoline-4,5-dione (**312**) in toluene.<sup>235</sup> It reacts with ethereal hydrazoic acid with effervescence to yield 3-hydroxy-5-phenyl-1,2,4-thiadiazole (**314**, 34%). Its further reaction with an excess of the isocyanate forms a bright red 1:1-adduct, possibly of structure **315**.<sup>236</sup> The products of the interaction of **313** and nitrosobenzene are the 5-substituted 1,2,4-thiadiazolin-3-ones (**316**, 58%); the fate of the eliminated oxygen is as yet not elucidated.<sup>237</sup> An alternative unequivocal synthesis of the products (**316**) by the oxidative cyclization of **317** confirms their structure.<sup>237</sup>



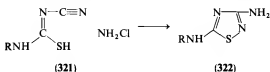
<sup>235</sup> J. Goerdeler and H. Horstmann, *Chem. Ber.* **93**, 671 (1960).

<sup>236</sup> J. Goerdeler and R. Weiss, *Chem. Ber.* **100**, 1627 (1967).

<sup>237</sup> J. Goerdeler and R. Schimpf, *Chem. Ber.* **106**, 1496 (1973).

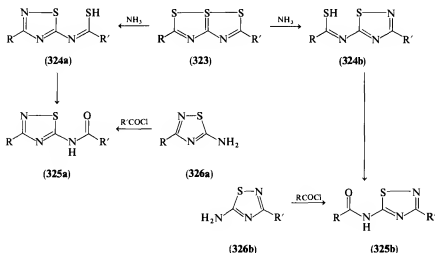
The interaction of thiobenzoyl isocyanates (318) and *N,N'*-diphenyl sulfur diimide yields 2,5-diaryl- $\Delta^4$ -1,2,4-thiadiazolin-3-ones (320) as very minor by-products (2%), presumably by way of the intermediate adducts (319).<sup>238</sup>

The condensation of alkali salts of *N*-substituted *N'*-cyanoisothioureas (321) and chloramine (prepared *in situ* from aqueous ammonia and chlorine) produces the substituted 3,5-diamino-1,2,4-thiadiazole (322). The reaction is an extension of the comparable ring closures involving potassium *S*-alkylcyanodithioimidocarbonates (see Section II.C.2.c).<sup>223,224</sup>



## 2. Synthesis from Trithiadiazapentalenes

2,5-Disubstituted 1,6,6a,*S*<sup>iv</sup>-trithia-3,4-diazapentalenes (323) are obtainable by the action of phosphorus pentasulfide on *N,N'*-diacyl-*S*-methylisothioureas in boiling xylene. They react with ammonia with elimination of hydrogen sulfide, to yield the substituted 2-thioaroylamido-1,2,4-thiadiazoles (324). Identically substituted starting materials (323, *R* = *R'*) produce single products (324a = 324b), but pairs of isomers (324a, 324b) arise from



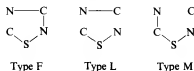
<sup>238</sup> O. Tsuge, S. Urano, and S. Mataka, *Heterocyclics* 5, 189 (1976).



unsymmetrical pentalenes (**323**,  $R \neq R'$ ) as expected. The products are desulfurized to the corresponding aroylamido compounds (**325**); the alternative synthesis of the latter from the authentic aminothiadiazoles (**326**) confirms the assigned structures, and the interpretation of the reaction sequence.<sup>239</sup>

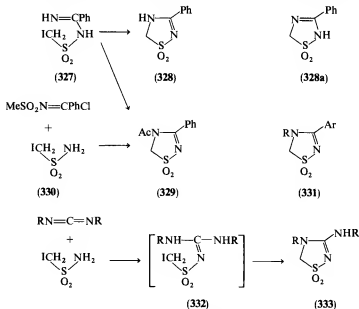
A group of syntheses of type E involving cyanodithioimidocarbonates (**280**) are described in Section II,C,2,c.

### E. TYPE F (L AND M) SYNTHESSES



#### *Synthesis of $\Delta^2$ -1,2,4-Thiadiazoline 1,1-Dioxides*

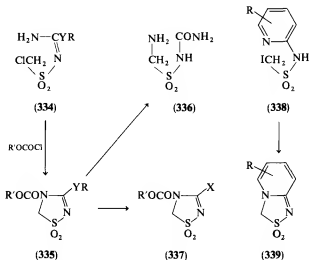
1,2,4-Thiadiazoline 1,1-dioxides (e.g., **328**, **331**) are obtainable by the cyclization by alkali of the readily accessible *N*-(iodomethylsulfonyl)benz-



<sup>239</sup> J. L. Deroque, M. Perrier, and J. Vialle, *Bull. Soc. Chim. Fr.*, 2062 (1968).

amidines (327). In the presence of acyl halides, simultaneous acylation results in 4-acyl-3-phenyl- $\Delta^2$ -1,2,4-thiadiazoline 1,1-dioxides (329). The assigned structures are supported by the alternative synthesis (Type L) of 329 (Ac = MeSO<sub>2</sub>) from iodomethanesulfonamide and the substituted methanesulfinimidoyl chloride (330); the evidence favors the  $\Delta^2$  (328) rather than the isomeric  $\Delta^3$  structure (328a).<sup>240</sup> The use of iodomethanesulfonylguanidines (332), produced *in situ* from iodomethanesulfonamide and carbodiimides, affords analogs incorporating 3-arylamino substituents (333).<sup>241</sup> The fragmentation of this ring system in the mass spectrometer appears to be initiated by expulsion of sulfur dioxide.<sup>241</sup>

In a closely related approach, chloromethylsulfonylisoureas (and thioureas) (334, Y = O, S) are simultaneously cyclized and acylated by chloroformates (R'OCOCl), resulting in a variety of 3,4-disubstituted  $\Delta^2$ -1,2,4-thiadiazoline 1,1-dioxides (335). Their 3-alkylthio group is displaceable by ammonia, furnishing the corresponding 3-amines (337, X = NH<sub>2</sub>), but ring opening to aminomethylsulfonylureas (336) occurs on more vigorous treatment. The products of the halogenation of 335 are the 3-chloro derivatives (337, X = Cl), which undergo further substitution reactions with nucleophiles.<sup>242,243</sup> The use of heterocyclic reactants supplying the amidino moiety in this synthesis



<sup>240</sup> A. Lawson and R. B. Tinkler, *J. Chem. Soc. C*, 652 (1969).

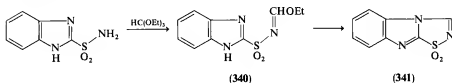
<sup>241</sup> A. Lawson and R. B. Tinkler, *J. Chem. Soc. C*, 1429 (1970).

<sup>242</sup> A. Etienne, A. LeBerre, G. Lonchambon, G. Lochey, and B. Cucumel, *Bull. Soc. Chim. Fr.*, 1580 (1974).

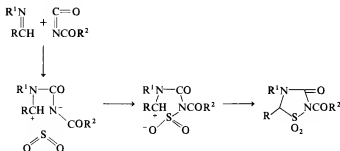
<sup>243</sup> A. Etienne, G. Lonchambon, and G. Lochey, French Patent 2,145,005 (1973) [*CA* 79, 53,333y (1973)].

results in fused structures: the pyridothiadiazole (**339**), for example, arises from **338** in this way.<sup>243</sup>

The 1,1-dioxide of 1,2,4-thiadiazolo[4,5-*a*]benzimidazole (**341**) is accessible by a synthesis (of Type M) involving the condensation of 2-sulfonamidobenzimidazole and ethyl orthoformate. The isolable intermediate ethoxymethylene derivative **340** yields the condensed tricyclic product **341** on cyclization.<sup>244</sup>



Another reaction (synthesis Type H) producing good yields of 1,1-dioxides of this ring system is the three-component interaction of azomethins, acyl isocyanates, and sulfur dioxide in anhydrous ether<sup>245</sup> (Scheme 8).



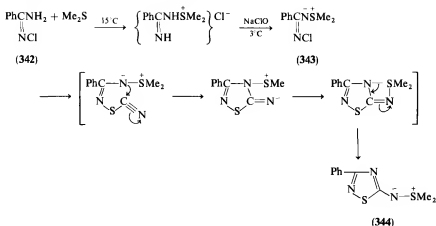
SCHEME 8

A remarkable formation of the 5-*S,S*-dimethylsulfilimine of 3-phenyl-1,2,4-thiadiazole (**344**) occurs on treatment of *N*-(*N*-chlorobenzimidoyl)-*S,S*-dimethylsulfilimine (**343**) with alkali thiocyanate. The starting material is accessible without difficulty from *N*-chlorobenzamidine (**342**). The reaction takes place exothermally in acetonitrile, and may possibly involve the mechanism shown in the scheme, which incidentally postulates a novel migration of the sulfonium group. According to the components from which the molecule is built up, the synthesis may also be included among those of type B.<sup>246</sup>

<sup>244</sup> B. Stanovnik and M. Tisler, *Arch. Pharm. (Weinheim, Ger.)* **300**, 322 (1967).

<sup>245</sup> B. A. Arbuzov, N. N. Zoboba, and N. R. Rubinova, *Izv. Akad. Nauk SSSR., Ser. Khim.*, 1438 (1975) (Engl. Transl., 1333).

<sup>246</sup> T. Fuchigami and K. Odo, *Bull. Chem. Soc. Jpn.* **50**, 1793 (1977).



## F. TYPE G SYNTHESSES

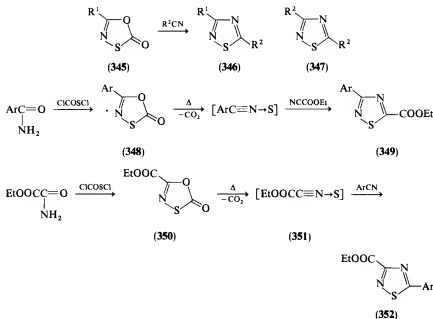
*Cycloadditions of Nitrile Sulfides to Nitriles*

Nitrile sulfides ( $\text{R}-\text{C}\equiv\text{N}\rightarrow\text{S}$ ) have recently become available as reactive intermediates in the thermolysis of 5-substituted 1,3,4-oxathiazol-2-ones (345); they may be trapped in 1,3-dipolar cycloadditions, resulting in *S,N*-heterocyclics.

Thus the cycloaddition of nitrile sulfides ( $\text{R}^1\text{CNS}$ ) to nitriles ( $\text{R}^2\text{CN}$ ) has provided a new general synthesis of 3,5-disubstituted 1,2,4-thiadiazoles (346). It is performed by the thermolysis of 345 at  $\sim 190^\circ\text{C}$  in an excess of the nitrile. Yields are moderate, but are satisfactory when aromatic nitrile sulfides interact with electrophilic nitriles. Minor amounts of 347, formed as by-products, may arise by sulfur transfer to the nitrile. The method is claimed to be useful in providing nonidentically disubstituted 1,2,4-thiadiazoles, in which there is no uncertainty about the position of the substituents.<sup>247</sup>

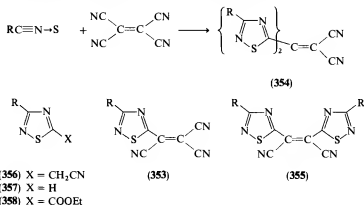
Ethyl cyanofornate reacts particularly smoothly with aryl nitrile sulfides, yielding 349.<sup>247</sup> The isomeric 5-aryl-1,2,4-thiadiazole-3-carboxylates (352) are formed analogously by the cycloaddition of ethoxycarbonylnitrile sulfide

<sup>247</sup> R. K. Howe and J. E. Franz, *J. Org. Chem.* **39**, 962 (1974).



(351) to aryl nitriles. The reagent (351) is generated and trapped *in situ* by thermolysis of the oxathiazolone (350) in an excess of the appropriate nitrile.<sup>248</sup>

1,3-Dipolar addition of nitrile sulfides to tetracyanoethylene produces mixtures of products, from which the mono- (353) and bis-1,2,4-thiadiazoles (354 and 355) are separable by selective solvent extraction. Equimolar



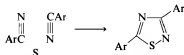
<sup>248</sup> R. K. Howe, T. A. Gruner, and J. E. Franz, *J. Org. Chem.* **42**, 1813 (1977); J. E. Franz and R. K. Howe (to Monsanto Co.), U.S. Patent 4,115,095 (1978) [*CA* **90**, 72,202y (1979)].

proportions of the reactants ( $R = Ph$ ) produce **353** almost exclusively (70%). Solvolysis of **353** degrades its side chain, yielding the ethyl ester (**358**) as the main product, together with some **356** and **357**. The bithiadiazoles (**355**) react analogously, but, because of their low solubility, do so more slowly.<sup>249</sup>

### G. TYPE H SYNTHESIS



An interesting and effective synthesis of 1,2,4-thiadiazoles is the direct condensation at high temperatures of aromatic nitriles and sulfur under the influence of suitable catalysts. Benzonitrile, for example, reacts with sulfur in the presence of tri-*n*-octylamine in closed vessels at 250°C to afford 3,5-diphenyl-1,2,4-thiadiazole in 75% yield. The effectiveness of the catalysts increases with their chain length, tri-*n*-octylamine being five times as active as triethylamine.<sup>250</sup>



A brief report has described the formation of the 1,2,4-thiadiazole ring system by the reaction of phosphorus tricyanide and sulfur dichloride: their spontaneous exothermic interaction yields 3,5-dichloro-1,2,4-thiadiazole, together with cyanuric chloride and other products.<sup>251</sup>

### H. TYPE J SYNTHESIS



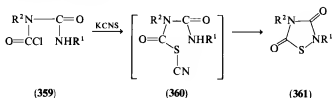
The action of potassium thiocyanate on substituted allophanic acid chlorides (**359**) in acetic acid, occurring with evolution of hydrogen cyanide, affords 2,4-disubstituted 1,2,4-thiadiazolidine-3,5-diones (**361**) readily in high

<sup>249</sup> J. E. Franz, R. K. Howe, and H. K. Pearl, *J. Org. Chem.* **41**, 620 (1976).

<sup>250</sup> W. Mack, *Angew. Chem., Int. Ed. Engl.* **6**, 1084 (1967).

<sup>251</sup> A. E. Barnett, P. Piotis, and B. Tittle, *J. Inorg. Nucl. Chem.* **38**, 1575 (1976).

yield. The reaction probably involves intermediates of type **360**; their rapid cyclization (to **361**) is thought to preclude other changes that thiocyanates might otherwise undergo.<sup>252</sup>



### I. UNCLASSIFIED SYNTHESIS

The interaction of sulfur nitride ( $\text{N}_4\text{S}_4$ ) and acetylenes is a synthetic route to 3,4-disubstituted 1,2,5-thiadiazoles. In some examples 1,2,4-thiadiazoles may arise as very minor by-products (e.g., 3-methoxycarbonyl-5-phenyl-1,2,4-thiadiazole from  $\text{PhC}\equiv\text{CCOOMe}$ ).<sup>253</sup>

### III. Physical Properties

The period covered by this review has seen a spectacular rise in the importance of physical techniques in the study of organic reactions. Its influence has been felt in the chemistry of 1,2,4-thiadiazoles no less than in other branches of the subject.

The main spectral methods are now routine tools, the results of which are inseparable from the total experimental evidence on which the interpretation of new reactions is based. Spectral information thus pervades the whole subject matter, and has been incorporated throughout the text, even though it is usually not specifically spelled out. However, investigations deliberately designed to gather and discuss spectral data require separate notice, as do those concerned with the mapping of the electron distribution in 1,2,4-thiadiazole. The vital contribution of X-ray crystallographic methods to recent progress in thiadiazole chemistry in general is briefly summarized separately.

<sup>252</sup> H. G. Werchan, G. Dittrich, and P. Held, German (East) Patent 121,519 (1976) [*CA* **87**, 23,294j (1977)].

<sup>253</sup> S. Mataka, K. Takahashi, Y. Yamada, and M. Tashiro, *J. Heterocycl. Chem.* **16**, 1009 (1979).

## A. SPECTRAL STUDIES

## 1. IR Spectra

A comparison of the IR spectra of 1,2,4-thiadiazoles with those of other five-membered N,S-heteroaromatic structures revealed no characteristic differences between them.<sup>254</sup> In agreement with previous assignments<sup>255,256</sup> prominent IR peaks were attributed as follows: to ring-skeletal vibrations ( $1560\text{--}1590$ ,  $1490\text{--}1550\text{ cm}^{-1}$ ), to ring-breathing and CH-in-plane deformations ( $1215\text{--}1270$ ,  $1080\text{--}1185$ ,  $1020\text{--}1050\text{ cm}^{-1}$ ), and to CH out-of-plane deformations ( $\sim 735$  and  $795\text{--}860\text{ cm}^{-1}$ ).<sup>254</sup> An examination of the IR spectra of a series of 3-amino-4-aryl-5-aryl(or alkyl)imino- $\Delta^2$ -thiadiazolines favors their 3-aminothiazoline- rather than the 3-iminothiadiazolidine structure.<sup>257</sup> The result is in accord with the general observation that in compounds of this type the double bond assumes a ring rather than an exocyclic position.<sup>59</sup> (cf. Hector's base, Section II.A.2.a). This conclusion is further supported by a study of the IR spectra of deuterated 5-membered heterocyclic compounds; that of deuterated 5-amino-3-phenyl-1,2,4-thiadiazole suggests the nonequivalence of the hydrogen atoms of the exocyclic amino group.<sup>258</sup>

## 2. NMR Spectra

Proton NMR spectral data appear throughout the literature, but a number of studies with specific objects are also on record. The  $^1\text{H}$  NMR spectra of a series of 3-amino-4-aryl-5-aryl(or alkyl)imino- $\Delta^2$ -thiadiazolines (including two 3-alkylamino homologs) support, as do the IR spectra (see above), their formulation as  $\Delta^2$ -ring-unsaturated 3-amines, rather than the tautomeric 3-imines.<sup>257</sup> The relation between the structures of 1,2,4-thiadiazolidines and their  $^1\text{H}$  NMR spectral solvent effects has been studied by measurement of the NMR chemical shift differences ( $\Delta_\nu$ ) of 39 derivatives in various solvents (e.g.,  $\text{C}_6\text{D}_6$ ,  $\text{CCl}_4$ ). For methyl or methylene groups attached to  $\text{sp}^2$ -hybridized nitrogen,  $\Delta_\nu$  correlates linearly with Hammett  $\sigma$  constants, for those attached to  $\text{sp}^3$ -hybridized nitrogen, with Taft  $\sigma^\circ$  constants. The

<sup>254</sup> C. N. R. Rao and R. Venkataraghavan, *Can. J. Chem.* **42**, 43 (1964).

<sup>255</sup> A. R. Katritzky, *Rev., Chem. Soc.* **13**, 353 (1959).

<sup>256</sup> A. R. Katritzky and A. P. Ambler, *Phys. Methods Heterocycl. Chem.* **2**, 232, 233, 237 (1963).

<sup>257</sup> C. P. Joshua and K. N. Rajasekharan, *Aust. J. Chem.* **28**, 591 (1975).

<sup>258</sup> H. Najer, J. Menin, and G. Petry, *C. R. Acad. Sci., Ser. C* **266**, 1587 (1968).



results were discussed in terms of conjugation between the nitrogen atoms, and the benzenoid substituents in the 1,2,4-thiadiazolidines.<sup>259</sup>

A comparison, by variable temperature NMR measurements, of the energy barrier to internal rotation of the dimethylamino group in five-membered heterocyclic structures has included the study of 5-dimethylamino-1,2,4-thiadiazole.<sup>260</sup> The compound is iso- $\pi$ -electronic with 4-dimethylaminopyrimidine, and is comparable in the positions of its nitrogen atoms. The observed closeness of their energy barriers reflects the analogies between cyclic isosteric compounds in which a sulfur atom replaces a  $-\text{CH}=\text{CH}-$  group. A variety of other aspects opened up by these measurements have been discussed.<sup>260</sup>

A study of the  $^{14}\text{N}$  NMR spectra of 45 azoles includes results for  $^{14}\text{N}$  chemical shifts of 1,2,4-thiadiazoles. The data are useful for distinguishing between isomeric azoles. A linear correlation is observed between the shifts and SCF-PPP-MO electron charge densities.<sup>261</sup>

### 3. Mass Spectra

The study of mass spectra and fragmentation patterns of 1,2,4-thiadiazoles has provided a background of information capable of helping in solving structural problems. Fragmentation of 3,5-disubstituted 1,2,4-thiadiazoles (**362**) occurs with loss of nitrile from the molecular ion, followed by extrusion of sulfur, and formation of nitrilium ion.<sup>262</sup>

3,5-Diamino-1,2,4-thiadiazole gives rise to a prominent molecular ion at  $m/e$  116. A peak appearing at  $m/e$  74 is indicative of the ejection of carbodiimide or cyanamide, possibly by the fragmentation pattern of Scheme 9.<sup>263</sup>

Similarly, substituted 5-amino-1,2,4-thiadiazoles (**364**) produce peaks corresponding to the molecular ion, and fragment to cyanamides ( $\text{RNHCN}$ ) and nitriles ( $\text{R'CN}$ , possibly via  $\text{R'CNS}$ ).<sup>264</sup> 3-Amino-isomers (**365**) behave analogously,<sup>263</sup> as does 3-amino-5-methylthio-1,2,4-thiadiazole.<sup>223</sup>

The mass spectra of a series of 3-amino-4-aryl-5-aryl(or alkyl)imino- $\Delta^2$ -1,2,4-thiadiazolines (**366**) have been interpreted in terms of fragmentation patterns, that are the result of fission of the molecules by routes a-c.<sup>257</sup> (see also Ref. 49). In an extension of this study to variously substituted 3,5-

<sup>259</sup> T. Kinoshita, S. Sato, Y. Furukawa, and C. Tamura, *Nippon Kagaku Kaishi*, 1256 (1978) [*CA* **90**, 5735m (1979)].

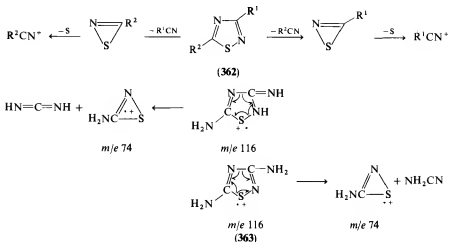
<sup>260</sup> T. Liljefors, *Org. Magn. Reson.* **6**, 144 (1974).

<sup>261</sup> L. Stefaniak, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **26**, 291 (1978).

<sup>262</sup> K. T. Potts and R. Armbruster, *J. Heterocycl. Chem.* **9**, 651 (1972).

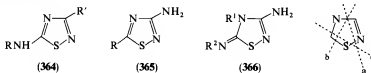
<sup>263</sup> A. Shoeb, S. P. Popli, and R. Gopalchhari, *Org. Mass Spectrom.* **7**, 555 (1973).

<sup>264</sup> A. H. Miller and R. J. Pancirow, *J. Heterocycl. Chem.* **8**, 163 (1971).



SCHEME 9

diamino-1,2,4-thiadiazoles, an attempt was made to establish guidelines for deriving from the mass-spectral data structural assignments to 1,2,4-thiadiazoles in general.<sup>265</sup> The 75 eV negative ion mass spectra of 2,4-disubstituted 3,5-diimino-1,2,4-thiadiazolidines have been studied and are claimed to differentiate better between isomeric compounds than do positive ion mass spectra.<sup>266</sup>



#### 4. Electron Distribution

A number of empirical<sup>267</sup> and semiempirical<sup>268</sup> studies of the electron distribution in all four thiadiazole ring systems have been reported; the

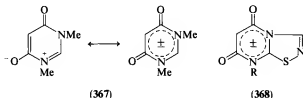
<sup>265</sup> C. P. Joshua and K. N. Rajasekharan, *Aust. J. Chem.* **30**, 563 (1977).

<sup>266</sup> T. Kinoshita, H. Nagaki, and C. Tamura, *Shitsuryo Bunseki* **25**, 109 (1977) [*CA* **87**, 101,539j (1977)].

<sup>267</sup> A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959); R. Zahradnik and J. Koutecky, *Collect. Czech Chem. Commun.* **26**, 156 (1961); E. Vincent and J. Metzger, *Bull. Soc. Chim. Fr.*, 2039 (1962).

<sup>268</sup> M. Gelus, P. M. Vay, and G. Berthier, *Theor. Chim. Acta* **9**, 182 (1967); R. Phan-Tan-Luu, L. Bouscasse, E. J. Vincent, and J. Metzger, *Bull. Soc. Chim. Fr.*, 3283 (1967); N. Bodor, M. Farkas, and N. Trinajstić, *Croat. Chem. Acta* **43**, 107 (1971).

results have been correlated with relevant data concerning thiazole and isothiazole. An investigation, by the LCAO- $\pi$ -molecular orbital (PPP) method, of the  $\pi$ -SCF-energy, charge distribution, and bond orders of compounds related to the mesionic 1,3-dimethylpyrimidine-4,6-dione (367), has included the condensed 1,2,4-thiadiazole (368, regarded as a mesionic purinone analog).<sup>269</sup> In a study of the propagation of errors in Hückel-Wheland molecular orbital calculations, uracil and the four thiadiazoles were chosen as test cases.<sup>270</sup>



A determination of the complete structure of the four thiadiazoles by double resonance modulation microwave spectroscopy has provided precise information of the bond distances and angles of each isomer. The results show that closest comparability exists between 1,2,4- and 1,2,5-thiadiazole on the one hand, and between the 1,2,3- and 1,3,4-isomers on the other.<sup>271</sup>

Helium photoelectron spectra of the four thiadiazoles have also been determined and have been interpreted by a comparison with those of thiophene and azole, and by *ab initio* MO calculations. Information is provided concerning the electronic charge distribution, and the electronic absorption spectra associated with these structures. The results suggest that 1,3,4-thiadiazole is significantly less aromatic than thiophene, while the other three isomers are more so.<sup>272</sup> An interesting comparison of thiadiazoles and oxadiazoles<sup>273</sup> by these techniques is also available (but does not include 1,2,4-oxadiazole). A study of the <sup>14</sup>N nuclear quadrupole resonance spectra of azoles has included that of the four thiadiazoles.<sup>274</sup> The spectra were obtained at 77 K, and the asymmetry parameters and coupling constants extracted. There is a high degree of agreement for the observed coupling constants derived from <sup>14</sup>N nuclear quadrupole resonance, or microwave

<sup>269</sup> R. A. Coburn, R. A. Carapellotti, and R. A. Glennon, *J. Heterocycl. Chem.*, **10**, 479 (1973).

<sup>270</sup> W. D. Moseley, J. Ladik, and O. Martensson, *Theor. Chim. Acta*, **8**, 18 (1967).

<sup>271</sup> O. L. Stiefvater, *Z. Naturforsch., A*, **31A**, 1681 (1976).

<sup>272</sup> M. H. Palmer, R. H. Findlay, J. N. A. Ridyard, A. Barrie, and P. Swift, *J. Mol. Struct.*, **39**, 189 (1977).

<sup>273</sup> M. H. Palmer, R. H. Findlay, and R. G. Egdell, *J. Mol. Struct.*, **40**, 191 (1977).

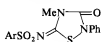
<sup>274</sup> M. Redshaw, M. H. Palmer, and R. H. Findlay, *Z. Naturforsch., A*, **34A**, 220 (1979).

spectra, and the *ab initio* calculations, both in magnitude and direction.<sup>274,275</sup> Variations in coupling constants with structure were discussed.<sup>274</sup>

## B. X-RAY ANALYSIS

In recent years, progress in the chemistry of 1,2,4-thiadiazoles has been greatly aided by the use of X-ray crystallographic techniques. The benefits have been of three kinds. First, the molecular dimensions and geometry of representative compounds have been accurately mapped, providing increasingly precise information concerning the structure of this ring system. These studies have been carried out almost exclusively with members of the partly or fully reduced series, rather than the heteroaromatic parent compounds. Second, accepted or doubtful structures have been modified or corrected in the light of these results. Finally, the method has on several occasions been the only means of elucidating the course of mystifying reactions, by solving at one stroke the structure of their products. When it is recalled that not a single X-ray analysis was quoted in the previous review,<sup>3</sup> the current frequent recourse to this powerful method is all the more impressive.

2,4-Dimethyl-1,2,4-thiadiazolidine-3,5-dithione is one of the simplest structures that has been analyzed.<sup>276</sup> The planarity of its 5-membered ring, and the observed bond lengths suggest that the molecule is highly conjugated over the S—CS—N—CS—N part of the ring (but excluding the N—S bond), so that a large number of canonical forms contribute to it. The angle at the ring sulfur is more acute than the others, being the usual pseudo right angle found in 5-membered hetero(sulfur) rings. The extranuclear 2-methyl and 5-thiono groups are distorted due to the absence of substituents on the ring sulfur.<sup>276</sup>



(369)



(370)



(371)



(372)

The iminothiadiazolidinone **369**<sup>277</sup> and the diimines **370**<sup>44,48</sup> and **371**<sup>46</sup> have nearly planar rings, with interatomic distances within the expected

<sup>275</sup> M. H. Palmer, A. J. Gaskell, and R. H. Findlay, *J. C. S. Perkin II*, 778 (1974); O. L. Stiefvater, *Chem. Phys.* **13**, 73 (1976).

<sup>276</sup> C. L. Raston, A. H. White, A. C. Willis, and J. N. Vargese, *J. C. S. Perkin II*, 1096 (1974).

<sup>277</sup> B. Deppisch, *Z. Crystallogr.* **143**, 112 (1976).

normal range for single bonds. In **372** (Alk = Me, CH<sub>2</sub>Ph) the thiadiazolidine rings show pronounced deviation from planarity, the sulfur being out of the plane of the other atoms.<sup>233</sup>

The X-ray technique has proved particularly valuable in indicating the formation of heteropentalenes, either as intermediates or final products, in several reactions of thiadiazoles. These applications are referred to in their proper place<sup>101,278,279</sup> throughout the text, as are examples of structural determinations of 1,2,4-thiadiazoles,<sup>84</sup> thiadiazolines ( $\Delta^{2,7,3}$ ;  $\Delta^{3,2,8,0}$ ), thiadiazolidines,<sup>29,30,52,96,98</sup> as well as condensed structures.<sup>105,164</sup>

## IV. Chemical Properties

The chemical reactions described in this Section are classified, as far as possible, according to the functions of the 1,2,4-thiadiazole structure, but some overlap has occurred when related results are summarized more effectively and briefly in one place. For the same reason some reactions have already been dealt with in the context of the syntheses.

### A. 1,2,4-THIA DIAZOLE AND HOMOLOGS

Because of the relative inaccessibility,<sup>272,281</sup> and limited stability<sup>281</sup> of the parent base,<sup>3</sup> studies of the nonfunctionalized ring system have employed homologs of 1,2,4-thiadiazole. Results concerning the quaternization, ring fission and ring expansion are applicable, in varying degree, to the ring system irrespective of its substituents. The behavior of alkyl-1,2,4-thiadiazoles provides further data for comparing the reactivity of identical substituents in the 3- and 5-position of the ring system.

#### 1. Quaternization

Diazoles are in principle capable of forming diquaternary salts without loss of aromaticity; however, it is difficult to introduce the second alkyl group, probably because quaternization of one ring nitrogen reduces the nucleophilicity of the other. Diquaternary salts of thiadiazoles of type **373**

<sup>278</sup> K. Akiba, S. Arai, and F. Iwasaki, *Tetrahedron Lett.*, 4177 (1978).

<sup>279</sup> K. Akiba, S. Arai, T. Tsuchiya, Y. Yamamoto, and F. Iwasaki, *Angew. Chem., Int. Ed. Engl.* **18**, 166 (1979).

<sup>280</sup> A. Kutoglu and H. Jepsen, *Chem. Ber.* **105**, 125 (1972).

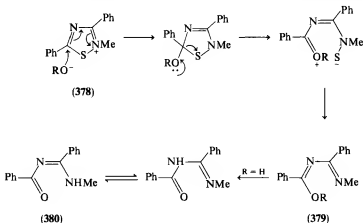
<sup>281</sup> J. Goerdeler, J. Ohm, and O. Tegtmeier, *Chem. Ber.* **89**, 1534 (1956).

and **374** and of other diazoles, have been obtained, however, by the use of specially reactive alkylating agents, viz., trialkyloxonium salts. The assigned structures are in accord with both spectroscopic and chemical data.<sup>282</sup>



Quaternization of 3,5-dimethyl- and 3,5-diphenyl-1,2,4-thiadiazole with methyl fluorosulfate produces, in the former case, the 4-methyl salt (**375**, Y = SO<sub>3</sub>F, 60%), in the latter a mixture of the 4- and 2-methyl isomers (**376**, **377**; Y = SO<sub>3</sub>F; 9 and 34%). The quaternization sites were established both by chemical and X-ray techniques. The predominant 2-quaternization in **377** is ascribed to the electronic and steric effects of the two phenyl groups flanking N4 in **377**.<sup>283</sup>

The action of nucleophiles on the quaternized 1,2,4-thiadiazoles ruptures the heterocyclic ring in every case. 2-Methyl-3,5-diphenyl-1,2,4-thiadiazolium fluorosulfate (**378**) is cleaved by alkoxide, giving *N*-(*N*-methylbenzimidoyl)-benzimidate (**379**); under the influence of hydroxide ions, reaction continues to the benzoylamidine stage (**380**). Comparable scissions occur with a variety of sulfur (sulfide, thiosulfate, benzenethiolate), nitrogen (amines, hydrazine, hydroxylamine) and carbon (cyanide, dicyanomethanide) nucleophiles. Ring opening occurs in every case, but the linear products corresponding



<sup>282</sup> T. J. Curphey and K. S. Prasad, *J. Org. Chem.* **37**, 2259 (1972).

<sup>283</sup> S. Crook and P. Sykes, *J. C. S. Perkin I*, 1791 (1977).

to **379** and **380** may undergo cyclization to other heterocyclic systems. In general, the nucleophilic reaction appears to be initiated at C5 by "hard" nucleophiles,<sup>284</sup> and at S1 by "soft" nucleophiles.<sup>283</sup>

Alkylation of diethyl  $\alpha$ -(3-*p*-chlorophenyl-1,2,4-thiadiazol-5-yl)malonate by successive treatment with sodium hydride and methyl iodide occurs at the extranuclear  $\alpha$ -carbon atom.<sup>285</sup>

## 2. Reductive Ring Cleavage

A variety of reducing agents cleave the 1,2,4-thiadiazole nucleus at its N—S bond by a reaction that may be regarded as the reverse of its synthesis by the oxidative cyclization of amidinothiono structures (see Section II.C.1). The resulting linear products are often isolable (e.g., amidinothioureas), but may recyclize to new ring structures (e.g., triazines), or decompose into simpler end-products (e.g., guanidines, thiocyanic acid). The relative ease with which the 1,2,4-thiadiazole ring is opened depends largely on the nature of its substituents. Scission occurs particularly readily in the reduced ring systems which have lost their aromatic character.<sup>3</sup> The numerous additional examples that have been described concern mostly 1,2,4-thiadiazoles incorporating functional substituents. In the condensed system **381**, the heteroring is readily cleaved by ascorbic acid, or by electrochemical reduction.<sup>199</sup>



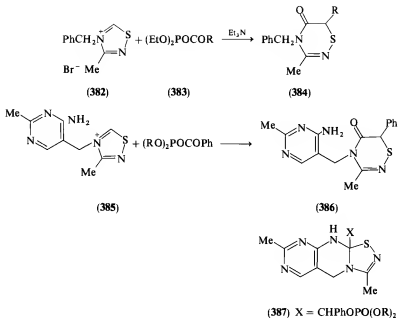
## 3. Ring Expansion

Certain 1,2,4-thiadiazoles undergo ring expansion on treatment with dialkyl acylphosphonates. Thus, the action of diethyl acetyl(or benzoyl)-phosphonates (**383**, R = Me, Ph) on 4-benzyl-3-methyl-1,2,4-thiadiazolium bromide (**382**) produces substituted 1,2,4-thiadiazines (**384**), albeit in low yield. The pyrimidyl analog (**385**, formally comparable with thiamin) behaves similarly, but a cyclization (to **387**) competes with the ring expansion (to **386**). The structure of these and other complex products, and the mechanism of their formation, were discussed in detail.<sup>286</sup>

<sup>284</sup> J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.* **84**, 19 (1962).

<sup>285</sup> D. M. O'Mant (to ICI Ltd.), German Patent 1,946,638 (1970), [*CA* **74**, 22,849p (1971)].

<sup>286</sup> A. Takamizawa and H. Hiroshi, *Chem. Pharm. Bull.* **18**, 1402 (1970).



#### 4. Methyl-1,2,4-thiadiazoles

5-Methyl-1,2,4-thiadiazoles (**392**) are accessible from the 5-chloro compounds (**388**) by two routes involving 5-malonic esters (see Scheme 10).<sup>287</sup> The initial replacement (**388**  $\rightarrow$  **389**) is effected in good yield by the action of sodiodiethyl malonate; the resulting 5-diethylmalonyl derivatives are remarkably resistant to alkaline hydrolysis, possibly because of their resonance stabilization as salts (**397**). Acid hydrolysis, performed on a small scale under strictly controlled conditions to prevent further decomposition, produces the 1,2,4-thiadiazol-5-ylacetic acids (**390**), and these are readily decarboxylated at 140–150°C to the 5-methyl homologs (**392**, R = Me, Et, Ph, SMe). Alternatively, the di-*tert*-butylmalonic esters (**391**) produce **392** in one operation on treatment with toluene-*p*-sulfonic-acetic acids. In contrast to previous syntheses of the 3,5-dimethyl homolog,<sup>288–290</sup> this approach provides 5-methyl-1,2,4-thiadiazoles bearing different 3-substituents.<sup>287</sup>

<sup>287</sup> J. Goerdeler and H. W. Hammen, *Chem. Ber.* **97**, 1134 (1964).

<sup>288</sup> W. Walter, *Justus Liebigs Ann. Chem.* **633**, 49 (1960).

<sup>289</sup> J. Goerdeler and H. Porrmann, *Chem. Ber.* **95**, 627 (1962).

<sup>290</sup> G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla, and A. Trede, *Angew. Chem.* **74**, 135 (1962).





Like their ultimate parent base, the 5-methyl-1,2,4-thiadiazoles (**392**) are colorless mobile thermally stable liquids of characteristic odor; the 3,5-dimethyl homolog is miscible with water in all proportions. Their spectral properties reflect their structural features; the  $^1\text{H}$  NMR spectrum of **392** ( $\text{R} = \text{Me}$ ) includes signals attributable to the 3- and 5-methyl groups at  $\delta 2.56$  and  $2.72$ , respectively. 5-Methyl-1,2,4-thiadiazoles form salts with mineral acids and 1:1-adducts with boron trifluoride and antimony pentachloride.<sup>287</sup>

Alkylation with methyl iodide or trialkyloxonium fluoborate occurs with some difficulty; by analogy with 5-amino-1,2,4-thiadiazoles,<sup>74</sup> the products are formulated as N4 quaternary salts. The 5-methyl group (in **392**) readily undergoes condensation with aromatic aldehydes to 5-styrylthiadiazoles (**393**). The action of carboxylic acid esters gives ethoxalyl derivatives (**394**) and that of isoamyl nitrite produces the oxime (**395**).<sup>287</sup>

It is significant that these reactions are restricted exclusively to the 5-methyl-group in 3,5-dimethyl-1,2,4-thiadiazole, even when an excess of the appropriate reagent is employed,<sup>287</sup> reflecting the superior reactivity of 5- compared with identical 3-substituents in the 1,2,4-thiadiazole structure.<sup>3</sup> The point is further illustrated in the metallation of the 3,5-dimethyl compound (**392**,  $\text{R} = \text{Me}$ ) with butyllithium; after further treatment with carbon dioxide, the 5-heteroarylacetic acid (**396**) is the sole product (62%).<sup>291</sup>

3,5-Diphenyl-1,2,4-thiadiazole, unlike several other phenyl-substituted five-membered (N,S) heterocyclic structures, does not undergo photolysis to benzonitrile sulfide,  $\text{PhC}=\text{N}$ , on being irradiated with UV light.<sup>292</sup>



## B. HALOGENO-1,2,4-THIADIAZOLES

### 1. 5-Halogeno-1,2,4-thiadiazoles

The reactivity of 5-halogen substituents in the 1,2,4-thiadiazole structure is well established<sup>3</sup>; nucleophilic substitution at this center has proved a convenient route to other 1,2,4-thiadiazoles, including 5-hydroxy, alkoxy, mercapto, alkylthio, amino, sulfonamido, hydrazino, hydroxylamino, and azido derivatives. All these reactions have been previously described.<sup>3</sup>

Kinetic measurements employing piperidine and other nucleophiles have illustrated strikingly and quantitatively the contrasting rates of replacement

<sup>291</sup> R. G. Micetich, *Can. J. Chem.* **48**, 2006 (1970).

<sup>292</sup> A. Holm and N. H. Toubro, *J. C. S. Perkin I*, 1445 (1978).

of chlorine in positions 5 and 3 in the 1,2,4-thiadiazole system. The substitutions are bimolecular, and of the first order with respect to each reactant involved.<sup>293</sup>

In a comparison<sup>294</sup> of the rates of substitution of halogen by primary and secondary amines in different heterocyclic systems, 5-chloro-3-phenyl-1,2,4-thiadiazole has proved one of the most reactive species. The replacement of a  $-\text{CH}=\text{CH}-$  moiety by sulfur in the heteroring greatly increases the rate at which the chloro substituent is displaced. Thus, the ratios of comparable velocity constants for the following pairs of compounds: chlorothiazole-chloropyridine, chlorobenzothiazole-chloroquinoline, and chlorothiadiazole-chloropyrimidine are 20, 350, and 400, respectively. Since the inductive effect of sulfur is small, the activation is probably due to a stabilization of the transition state.<sup>294</sup> Another kinetic study of the substitution of the halogen in 3-alkylmercapto-5-chloro-1,2,4-thiadiazoles by piperidine or aniline has shown that their reactivity is comparable with that of dimethoxychloro-*s*-triazine, and that the *S*-alkyl substituent exerts no appreciable effect.<sup>134</sup>

Among nucleophilic replacements, ammonolysis and aminolysis have been most frequently studied and have provided a wide range of 5-amino-1,2,4-thiadiazoles.<sup>120,124,294-300</sup> Starting materials incorporating a variety of 3-substituents have been successfully employed.<sup>297</sup> The use of 1-aminoanthraquinones affords 1-(3-phenyl-1,2,4-thiadiazole-5-amino)anthraquinones, useful as vat dyes for cotton.<sup>301</sup> The action of *N,N*-dimethylpropane-1,3-diamine on 5-chloro-3-trichloromethyl-1,2,4-thiadiazole gives moderate yields of three substitution products (398-400), the last being apparently formed by an unusual replacement of the distal methyl group of 399. The bithiadiazole (399) is of interest as the most promising member of a series of effective antimalarial compounds.<sup>302</sup> Nucleophilic replacement by  $\beta$ -aminoethanol involves the amino group preferentially, yielding 5-(2-hydroxy-

<sup>293</sup> J. Goerdeler and K. H. Heller, *Chem. Ber.* **97**, 225, 238 (1964), and references given therein.

<sup>294</sup> H. Grube and H. Suhr, *Chem. Ber.* **102**, 1570 (1969).

<sup>295</sup> M. Zbirovsky, L. Puncchar, J. Stanek, and J. Zermanek, Czech Patent 120,541 (1966) [*CA* **68**, 69,001x (1968)].

<sup>296</sup> I. Saikawa, T. Wada, Y. Suzuki, and A. Takai (to Toyama Chemical Industry Co.), Japanese Patent 67/8,028 (1967) [*CA* **67**, 54,137b (1967)].

<sup>297</sup> T. Noguchi, Y. Hashimoto, T. Mori, S. Kano, and K. Miyazaki, *Yakugaku Zasshi* **88**, 1437 (1968) [*CA* **70**, 77,873q (1969)].

<sup>298</sup> F. Troxler and G. Bormann (to Sandoz A.G.), Swiss Patent 497,453 (1970) [*CA* **75**, 5906h (1971)].

<sup>299</sup> M. Zbirovsky, J. Myska, and J. Stanek, *Collect. Czech Chem. Commun.* **36**, 4087 (1971).

<sup>300</sup> P. Bracha and M. Luwisch (to Makhteshim Chemical Works), German Patent 2,154,852 (1972) [*CA* **77**, 114,411e (1972)]; Israel Patent 35,743 (1974) [*CA* **83**, 43,332r (1975)].

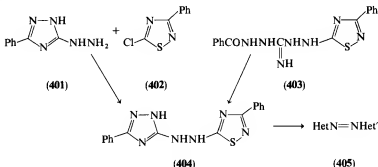
<sup>301</sup> H. Weissauer (to BASF A.G.), German Patent 1,907,407 (1970) [*CA* **74**, 4680x (1971)].

<sup>302</sup> E. F. Eislagar, J. Johnson, and L. M. Werbel, *J. Heterocycl. Chem.* **10**, 611 (1973).

ethylamino)-1,2,4-thiadiazoles.<sup>303</sup> Anthranilic acid<sup>304</sup> and piperazines<sup>305</sup> also act as effective nucleophiles.



The action of hydrazine,<sup>125,127</sup> hydroxylamine,<sup>125,127</sup> and guanidine<sup>306</sup> proceeds as expected. 3-Phenyl-5-hydrazino-1,2,4-triazole (**401**) reacts with **402** to yield the hydrazinothiadiazole (**404**); this unequivocal synthesis confirms the course of the alternative formation of **404** by the cyclization of 1-benzoyl-5-(3-phenyl-1,2,4-thiadiazol-5-yl)diaminoguanidine (**403**). Air oxidation of **404** in the presence of alkali produces the azo compound **405**.<sup>307</sup>



The replacement of 5-chloro substituents by oxygen functions has been effected by the use of ethylene glycol and its homologs,<sup>125,126</sup> glycidol (2-hydroxymethyloxiran),<sup>308</sup> and sodium phenoxide.<sup>309</sup> Prolonged treatment of 3-substituted 5-chloro-1,2,4-thiadiazoles with boiling acetic acid yields the corresponding  $\Delta^2$ -1,2,4-thiadiazolin-5-ones.<sup>310</sup>

<sup>303</sup> H. Berger, R. Gall, K. Stach, W. Voemel, and W. Sauer (to Boehringer Mannheim G.m.b.H.), German Patent 2,202,385 (1973) [CA 79, 105,285f (1973)].

<sup>304</sup> E. Falch, J. Weis, and T. Natvig, *J. Med. Chem.* **11**, 608 (1968).

<sup>305</sup> G. Regnier, R. Canevari, M. Laubie, and J. C. Poignant (to Science Union et Cie.), German Patent 2,758,314 (1978) [CA 89, 180,042j (1978)].

<sup>306</sup> D. F. Jones and K. Oldham (to ICI Industries), European Patent Appl. 3,640 (1979) [CA 92, 94,405k (1980)].

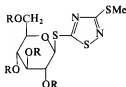
<sup>307</sup> H. Gehlen and R. Neumann, *J. Prakt. Chem.* **311**, 213 (1969).

<sup>308</sup> Y. Antonio, C. Camargo, E. Galeazzi, J. Iriarte, M. Guzman, J. M. Muchowski, K. Gerrity, F. Liu, L. M. Miller, and A. M. Strosberg, *J. Med. Chem.* **21**, 123 (1978).

<sup>309</sup> E. Smith (to Olin Corp.), U.S. Patent 3,573,317 (1971) [CA 74, 141,808j (1971)].

<sup>310</sup> R. F. W. Raetz and J. F. Cronan (to Ansul Co.), U.S. Patent 3,574,226 (1971) [CA 74, 141,819p (1971)].

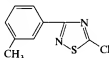
5-Alkylthio-1,2,4-thiadiazoles are obtained by treatment of the appropriate chloro compounds with sodium alkylthiols.<sup>311,312</sup> The production of thioglycosides (**406**) is an interesting application of this replacement. Thus, 5-chloro-3-methylthio-1,2,4-thiadiazole reacts with sodium thioglucose or its tetraacetyl derivative to yield 3-methylthio-5-( $\beta$ -D-glucopyranosyl)thio-1,2,4-thiadiazole (**406**).<sup>313</sup>



(406) R = H or Ac

Nucleophilic replacement of a 5-bromo by an isothiurea group and careful alkaline hydrolysis of the resulting 5-alkylthiuronium salt is a method of preparing 1,2,4-thiadiazole-5-thione unsubstituted in its 3-position. An alternative procedure<sup>314</sup> is the successive treatment of 5-chloro-1,2,4-thiadiazoles with trisodium thiophosphate, and acid-catalyzed decomposition of the intermediate salt [HetSPO(ONa)<sub>2</sub>] *in situ*.<sup>315</sup>

5-Chloro-1,2,4-thiadiazoles are also a useful source of 5-alkyl and -aryl sulfones and 5-alkyl and -aryl thiols; these are readily obtainable by the action of the appropriate sodium sulfinates or thiols.<sup>316-318</sup> The action of



(407)

<sup>311</sup> M. H. Rosen and H. M. Blatter (to Ciba-Geigy Corp.), U.S. Patent 3,692,794 (1972) [CA 77, 152,239n (1972)].

<sup>312</sup> J. H. Parsons (to Fisons Ltd.), German Patent 2,050,346 (1971) [CA 75, 36,051e (1971)].

<sup>313</sup> G. Wagner and B. Dietzsch, *Pharmazie* **33**, 764 (1978).

<sup>314</sup> Procedure: T. T. Conway, A. Shoeb, and L. Bauer, *J. Pharm. Sci.* **57**, 455 (1968).

<sup>315</sup> G. Lacasse and J. M. Muchowski, *Can. J. Chem.* **51**, 2353 (1973).

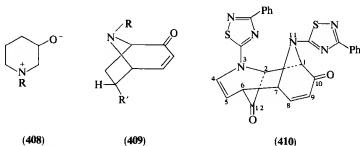
<sup>316</sup> A. Kaji, S. Kano, Y. Miyazaki, K. Hashimoto, and T. Noguchi, Japanese Patent 25,382 (1963) [CA 60, 5512 (1964)].

<sup>317</sup> J. Bader, H. Hamboeck, E. Sturm, and A. G. Weiss (to Ciba-Geigy A.G.), German Patents 2,242,186-7 (1973) [CA 79, 5344f; 78, 147,973p (1973)]; Swiss Patent 562,003 (1975) [CA 83, 92,370k (1975)]; Ciba-Geigy A.G., French Patent 2,151,037 (1973) [CA 79, 103,875z (1973)].

<sup>318</sup> J. Bader, H. Hamboeck, E. Sturm, and A. G. Weiss (to Ciba-Geigy A.G.), German Patent 2,242,185 (1973) [CA 78, 159,608m (1973)].

chlorine on **407** converts its 3'-methyl to the 3'-trichloromethyl group, the 1,2,4-thiadiazole moiety remaining unaffected<sup>319</sup>; other comparable chlorinations are on record.<sup>320</sup>

In a systematic examination of the suitability of 3-hydroxypyridine as a precursor in the synthesis of tropolones, the base was N-substituted, and the resulting betaines condensed with dipolarophiles. Among others, the betaine **408** was prepared from 5-chloro-3-phenyl-1,2,4-thiadiazole for this purpose. It dimerizes to the syn dimer **410**, but when generated in the presence of dipolarophiles (e.g., acrylonitrile), undergoes  $[4\pi + 2\pi]$  thermal addition to yield the endo adduct (e.g., **409**). However, neither the thiadiazolyl nor analogous substituents fulfilled the requirement of making the pyridine moiety sufficiently susceptible toward cycloaddition, and of being readily detached after this reaction.<sup>321</sup>



R = 3-Phenyl-1,2,4-thiadiazol-5-yl

## 2. 3,5-Dichloro-1,2,4-thiadiazoles

3,5-Dichloro-1,2,4-thiadiazole, first obtained from the 3,5-dimercapto analog (see Section IV,D,2) is a lachrymatory liquid, with spectral properties in accord with its structure. Its 5-halogen substituent displays the expected<sup>3</sup> higher reactivity, being selectively replaced by nucleophilic reagents (e.g., piperidine); prolonged treatment (100 h) with an excess of aniline, however, yields 3,5-dianilino-1,2,4-thiadiazole.<sup>147</sup>

<sup>319</sup> E. Hahn and M. Seefelder (to BASF A.G.), French Patent 1,469,787 (1967) [*CA* **68**, 49,634c (1968)].

<sup>320</sup> J. Krenzer (to Velsicol Chemical Corp.), U.S. Patent 3,534,057 (1970) [*CA* **74**, 53,805a (1971)].

<sup>321</sup> A. R. Katritzky, J. Banerji, A. Boonyarakvanich, A. T. Cutler, N. Dennis, S. Q. A. Rizvi, G. J. Sabongi, and H. Wilde, *J. C. S. Perkin I*, 399 (1979).

## C. HYDROXY-1,2,4-THIA DIAZOLES

The acylation of 3- and 5-hydroxy-1,2,4-thiadiazoles has been the subject of several investigations. In an extensive study<sup>322</sup> of the action of electrophiles on 3-hydroxy-1,2,4-thiadiazoles, replacements of two kinds were established. "Hard" electrophiles<sup>323</sup> (including acid chlorides of carboxylic, sulfonic, phosphonic, and sulfamic acids) attack the hydroxyl oxygen, giving predominantly 3-acyl derivatives (**411**). In aprotic solvents, "soft"<sup>323</sup> electrophiles (including isocyanate esters<sup>322,324</sup> and acid anhydrides) attack the N2 position, yielding derivatives (e.g., **412**) of the 1,2,4-thiadiazolin-3-ones. The nature of the 5-substituent is of little consequence; mixtures of both **411** and **412** are occasionally obtained. The parallel behavior, in this respect, of corresponding compounds of the 3-hydroxyisothiazole and 1,2,4-thiadiazole series is noteworthy.<sup>322</sup> Both 3- and 5-hydroxy-1,2,4-thiadiazoles readily form sulfonic acid esters on being treated with methanesulfonyl chloride.<sup>325</sup>



(411)



(412)

Acylation of 3-alkyl-5-hydroxy(or mercapto)-1,2,4-thiadiazoles by ethyl chloroformate or acid chlorides which attack the N4 ring nitrogen, resulting in **413** (X = O, S).<sup>326</sup> An O → N4 migration of an alkyl group occurs to a limited extent upon thermolysis (vacuum distillation) of the 5-(β-hydroxyethoxy) compound **414**.<sup>125</sup> In a projected synthesis of 1,2,4-thiadiazole analogs of pyrimidine nucleosides, the applicability of the Hilbert-Johnson reaction<sup>327</sup> has been examined.<sup>328</sup> 3,5-Diethoxy-1,2,4-thiadiazole reacts only slowly with benzyl bromide in boiling acetonitrile, but rapidly with chloromethyl benzyl ether at room temperature. Of the possible structures (**416**, **417**) of the product, the former is favored on mass-spectral evidence. Attempted debenzoylation (of **416**) under reductive or hydrolytic conditions ruptured the heteroring.<sup>328</sup>

<sup>322</sup> L. Taliani and J. Peronet, *J. Heterocycl. Chem.* **16**, 961 (1979).

<sup>323</sup> R. G. Pearson (ed.), "Hard and Soft Acids and Bases". Dowden, Hutchinson & Ross, Inc., Stroudsburg, Pennsylvania, 1973; Tse-Lok Ho, "Hard and Soft Acids and Bases Principle in Organic Chemistry", Academic Press, New York, 1977.

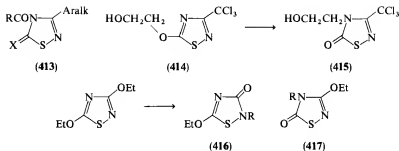
<sup>324</sup> J. Perronnet, L. Taliani, and A. Teche (to Roussel UCLAF), German Patent 2,617,339 (1976) [*CA* **86**, 43,709f (1977)].

<sup>325</sup> B. Boehner, D. Dawes, W. Meyer, H. Kristinsson, and K. Ruefenacht (to Ciba-Geigy A.G.), German Patent 2,428,204 (1975) [*CA* **82**, 156,321j (1975)].

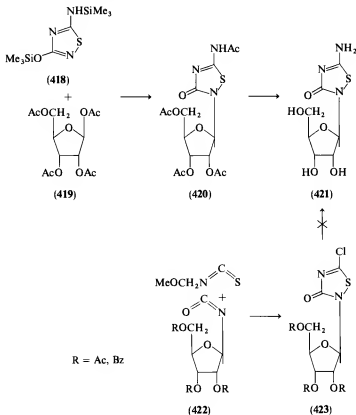
<sup>326</sup> E. H. Pommer, H. Hagen, and H. Fleig (to BASF A.G.), German Patent 2,405,324 (1975) [*CA* **84**, 31,079w (1976)].

<sup>327</sup> Review: J. Pliml and M. Prystas, *Adv. Heterocycl. Chem.* **8**, 115 (1967).

<sup>328</sup> G. Koomen and U. K. Pandit, *Heterocycles* **3**, 539 (1975).



The synthesis of an interesting 1,2,4-thiadiazole nucleoside has been achieved by the following route: 5-amino-3-hydroxy-1,2,4-thiadiazole, in which the substituents are blocked (418) by silylation,<sup>329</sup> is condensed with 1,2,3,5-tetra-O-acetyl- $\beta$ -D-ribofuranose (419), in 1,2-dichloroethane in the



<sup>329</sup> E. Wittenburg, *Z. Chem.* 4, 303 (1964).



presence of stannic chloride,<sup>330</sup> and affords **420** in 60% yield. The deacetylation (of **420**) may be performed selectively in stages; prolonged treatment with methanolic sodium methoxide produces the parent nucleoside (**421**, 48%).<sup>331</sup> In another approach, 2,3,5-tri-O-acetyl(or benzoyl)- $\beta$ -D-ribofuranosyl isocyanate (**422**) and methoxymethyl isothiocyanate were successfully condensed by the action of chlorine (see Section II.B.4.b), yielding **423**; however, these products decomposed during their attempted conversion to **421**.<sup>331</sup>

### Phosphoric and Phosphonic Esters

Hydroxy-1,2,4-thiadiazoles readily form esters with phosphoric acid and its various analogs. Because of the pesticidal properties of these organophosphorus compounds, and their reported relatively low toxicity to warm-blooded animals, a large volume of preparative work has been undertaken. The patent literature exemplifies almost the full range of possible phosphoric and phosphonic acid derivatives, and their thio analogs. For their production, a hydroxy-1,2,4-thiadiazole is condensed with the phosphoro- or phosphonochloridic ester (**426** or **429**), in the presence of a base.<sup>332-336</sup> Alternatively, a halogeno-1,2,4-thiadiazole is allowed to react with the appropriate free acid (**424** or **427**).<sup>337-341</sup> The use of mercapto-1,2,4-thiadiazoles, or of the

<sup>330</sup> U. Niedballa and H. Vorbrueggen, *Angew. Chem., Int. Ed. Engl.* **9**, 461 (1970); *J. Org. Chem.* **36**, 3672 (1974).

<sup>331</sup> G. R. Revankar and R. K. Robins, *J. Heterocycl. Chem.* **13**, 169 (1976); U.S. Patent 4,093,624 (1978) [*CA* **89**, 180,309b (1978)].

<sup>332</sup> C. Fest (to Bayer A.G.), German Patent 1,193,953 (1965) [*CA* **63**, 16,384 (1965)].

<sup>333</sup> M. D. Barker, J. Wood, and E. N. Binnie (to Shell International N.V.), German Patent 2,236,459 (1973) [*CA* **78**, 111,326r (1973)].

<sup>334</sup> W. Meyer, B. Boehner, and D. Dawes (to Ciba-Geigy A.G.), German Patent 2,418,363 (1974) [*CA* **82**, 31,328k (1975)]; *Kem.-Kemi* **1**, 585 (1974) [*CA* **82**, 107,475d (1975)].

<sup>335</sup> J. Perronnet and L. Taliani (to Roussel-UCLAF), German Patent 2,450,815 (1975) [*CA* **83**, 97,307e (1975)]; Roussel-UCLAF, French Patent 2,287,454 (1976), [*CA* **86**, 89,828x (1977)]; 2,345,458 (1977) [*CA* **89**, 24,322v (1978)].

<sup>336</sup> Ciba-Geigy A.G., Japanese Patent 74/75,733 (1974) [*CA* **85**, 73,464u (1976)].

<sup>337</sup> W. Lorenz (to Bayer A.G.), Belgian Patent 635,443 (1964) [*CA* **61**, 16,096 (1964)]; German Patent 1,445,709 (1971) [*CA* **75**, 36,143m (1971)].

<sup>338</sup> R. F. W. Raetz and J. F. Cronan (to Ansul Co.), U.S. Patent 3,574,223 (1971) [*CA* **75**, 20,409s (1971)].

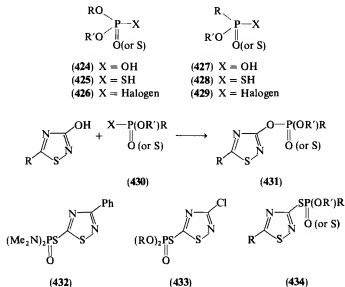
<sup>339</sup> E. J. Gaughan (to Stauffer Chemical Co.), U.S. Patent 3,632,597 (1972) [*CA* **76**, 99,677e (1972)]; U.S. Patent 3,755,571 (1973) [*CA* **80**, 34,393x (1974)].

<sup>340</sup> M. D. Barker (to Shell International N.V.), German Patent 2,154,443 (1972) [*CA* **77**, 48,472x (1972)].

<sup>341</sup> B. Boehner, D. Dawes, W. Meyer, and E. Sturm (to Ciba-Geigy A.G.), German Patent 2,500,485 (1975) [*CA* **84**, 44,068s (1976)].

requisite thiophosphoric acid derivatives (**425** or **428**), affords the sulfur analogs (e.g., **434**), of which an even larger number have been described.<sup>337-341</sup> Both the 3-position<sup>333-336,338,340,341</sup> and the 5-position<sup>332,337,339,340</sup> of 1,2,4-thiadiazole may be modified in this way.

The interaction of a thiadiazolylsulfenyl chloride and a dialkyl sulfite provides an alternative route to the dialkylthiophosphoric esters (e.g., **433**).<sup>342</sup> A further structural variation is introduced by the use of phosphorodiamidic chlorides [e.g.,  $(\text{Me}_2\text{N})_2\text{POCl}$ ], leading to compounds of type **432**.<sup>343</sup>



#### D. MERCAPTO-1,2,4-THIA DIAZOLES

The properties of mercapto-1,2,4-thiadiazoles, particularly those of the interesting 3,5-dimercapto compound (perthiocyanic acid) have been established in fair detail for some time<sup>3</sup>; recent work has in the main been supplementary in nature. Attention is drawn to the extensive use of 5-mercapto-1,2,4-thiadiazoles in the production of cephalosporin derivatives; this is briefly reviewed separately at the end of this Section.

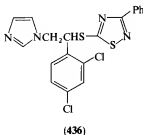
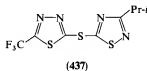
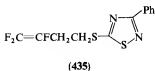
<sup>342</sup> K. Nishio, T. Kikugaki, T. Nishihara, and K. Takita (to Kumiai Chemical Industry Co.), Japanese Patent 73/99,343 (1973) [*CA* **81**, 10,478y (1974)].

<sup>343</sup> N. V. Philips Gloeilampenfabrieken, British Patent 947,485 (1964) [*CA* **60**, 14,514 (1964)].

## 1. 3- and 5-Mercapto-1,2,4-thiadiazoles

The mercury salt of 3-mercapto-1,2,4-thiadiazole (mercuric 1,2,4-thiadiazole 3-thiolate) is obtainable by cleaving the corresponding disulfide with mercury, and is convertible to the unstable sodium 3-thiolate by the action of sodium sulfide.<sup>315</sup>

The action of trifluorobutenyl bromide ( $\text{CF}_2=\text{CFCH}_2\text{CH}_2\text{Br}$ ) on 3-phenyl-5-mercapto-1,2,4-thiadiazole and numerous analogs produces 5-(3,4,4-trifluoro-3-butenyl)thio derivatives (**435**), which are useful nematocides.<sup>344</sup> The 5-alkylthio compound (**436**) is the product of the S-alkylation using 1-( $\beta$ -chloro-2,4-dichlorophenyl)imidazole.<sup>345</sup> The formation of the monosulfide (**437**) from 3-isopropyl-5-mercapto-1,2,4-thiadiazole occurs under standard conditions.<sup>346</sup>



3-Methyl(and phenyl)-5-mercapto-1,2,4-thiadiazoles are converted by chloromethyl thiocyanate to the thiomethyl thiocyanates ( $\text{RSCH}_2\text{SCN}$ ) and are thence oxidized to the corresponding sulfinyl and sulfonyl thiocyanates with 3-chloroperoxybenzoic acid or hydrogen peroxide.<sup>347</sup> 3-Alkyl-

<sup>344</sup> M. E. Brokke (to Stauffer Chemical Co.), U.S. Patents 3,513,172 (1970); 3,654,293, 3,666,818, 3,692,912, 3,697,536, 3,700,668 (1972); 3,780,050 (1973); 3,891,662 (1975); Appl. B 354,979 (1975) [*CA* **73**, 35,381j (1970); **77**, 19,542q, 88,467f (1972); **78**, 29,777e, 43,464g, 58,452a (1973); **80**, 82,988s (1974); **83**, 131,611m, 193,289w (1975)].

<sup>345</sup> D. A. Cox, G. E. Gymer, and B. Shroott (to Pfizer Inc.), British Patent 1,511,390 (1978) [*CA* **89**, 215,405j (1978)].

<sup>346</sup> J. H. Reisdorff, A. Haberkorn, M. Plempel, and W. Stendel (to Bayer A.G.), German Patent 2,533,605 (1977) [*CA* **86**, 171,462g (1977)].

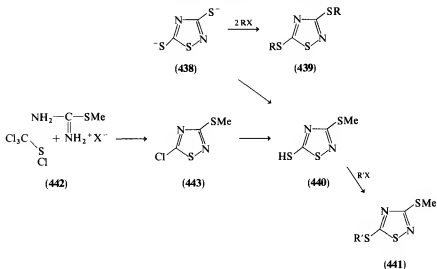
<sup>347</sup> A. G. M. Willems, A. Tempel, D. Hamminga, and B. Stork, *Recl. Trav. Chim. Pays-Bas* **90**, 97 (1971); N. V. Philips Gloeilampenfabrieken, French Patent 1,592,562 (1970) [*CA* **75**, 5475s (1971)].

thio-<sup>114,115</sup> and 5-alkyl(or aryl)thio-1,2,4-thiadiazoles<sup>311,348</sup> have been repeatedly oxidized to sulfoxides<sup>348</sup> or sulfones<sup>114,115,311,348</sup> under the influence of the same oxidizing agents.

Phosphoro and phosphono thioates and dithioates which are formally derived from mercapto-1,2,4-thiadiazoles, but are usually prepared from the halogeno compounds, are described together with their oxygen analogs (see Section IV.C).

## 2. 3,5-Dimercapto-1,2,4-thiadiazole (Perthiocyanic Acid)

The alkylation of perthiocyanic acid has been the subject of a number of studies. 3,5-Dialkylthio-1,2,4-thiadiazoles (**439**) are well-known,<sup>3</sup> but mono-alkyl derivatives have been investigated only recently.<sup>349</sup> The interaction of equimolecular quantities of sodium perthiocyanate (**438**) and methyl iodide produces the 3-methylthio (**440**, 28%) and 3,5-di(methylthio) compounds (**439**, R = Me, 27%) side by side. The structure of the former (**440**) is established<sup>349</sup> by its unequivocal synthesis (**442** → **443** → **440**) by Goerdeler's method.<sup>208</sup> Mixed 3,5-dialkylthio-1,2,4-thiadiazoles [**441**, e.g., R' = 2,4-(NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, PhCH<sub>2</sub>, C<sub>10</sub>H<sub>21</sub>] are accessible from **440** by further alkylation.<sup>350</sup> Other 3,5-dialkylthio-1,2,4-thiadiazoles have been prepared



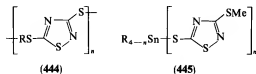
<sup>348</sup> J. H. Parsons (to Fisons Ltd.), German Patent 2,142,913 (1972) [CA 77, 5476j (1972)].

<sup>349</sup> R. Seltzer, *J. Org. Chem.* **34**, 2562 (1969).

<sup>350</sup> R. Seltzer (to M. & T. Chemicals Inc.), U.S. Patent 3,597,426 (1971) [CA 75, 110,325r (1971)].

from **438** by the action of chloromethylthiocyanate,<sup>351</sup> bromochloromethane,<sup>352</sup> and 1-chloro-2,4-dinitrobenzene<sup>353</sup> (see also Ref. 147).

The interaction of sodium perthiocyanate (**438**) and suitable bifunctional dihalides readily produces polymers (**444**) which are claimed to be useful catalysts in the production of polyurethane foams. The use of 1,4-di(chloromethyl)benzene in ethanol, for example, gives **444** ( $R = p\text{-CH}_2\text{C}_6\text{H}_4\text{CH}_2$ , terminating in  $p\text{-CH}_2\text{C}_6\text{H}_4\text{CH}_2\text{OEt}$ , mol wt 2960) in 90% yield.<sup>354</sup> 5-Mercapto-3-methylthio-1,2,4-thiadiazole yields the tin-containing derivatives **445** ( $R = \text{Bu, Ph, or cyclohexyl; } n = 1\text{--}3$ ) on treatment with alkyltin halides in tetrahydrofuran.<sup>355</sup>



**Chlorolysis.** The action of chlorine on mercapto-1,2,4-thiadiazoles yields sulfenyl chlorides, sulfonyl chlorides, or chloro compounds, depending on the nature of the starting materials and the experimental conditions.<sup>147</sup> Thus treatment of 3-*tert*-butylthio-1,2,4-thiadiazole with one mole of chlorine yields bis(1,2,4-thiadiazol-3-yl) disulfide (**446**) as a stable colorless solid. An excess of chlorine converts this to the 3-sulfonyl chloride (**447**), and further, with loss of sulfur dioxide, to the 3-chloro compound (**448**). Under appropriate conditions, the chlorolysis (to **448**) may be performed in one operation (45%). The 3-sulfonyl chloride (**447**) yields sulfonamides nearly quantitatively; the 3-chloro substituent in **448** is relatively inert (see Section IV.B).<sup>147</sup>

A series of comparable bifunctional products arise similarly from the 3,5-dimercapto compound.<sup>147</sup> Barium perthiocyanate (**438**) may serve as the source of most of these, but yields are only moderate. Chlorolysis of bis(5-chloro-1,2,4-thiadiazol-3-yl) disulfide<sup>356</sup> provides the 5-chloro-3-sulfonyl (and sulfenyl) chlorides (**451, 450**); the latter is also a minor product of the action of chlorine on lead thiocyanate. 3,5-Dichloro-1,2,4-thiadiazole (**452**) is obtained most advantageously by the chlorolysis of the 3,5-bisthioethers

<sup>351</sup> R. G. Pews, C. T. Goralski, and G. A. Burk (to Dow Chemical Co.), U.S. Patent 3,888,869 (1975) [CA 83, 114,421g (1975)].

<sup>352</sup> C. T. Goralski and G. A. Burk (to Dow Chemical Co.), U.S. Patent 4,094,880 (1978) [CA 89, 180,016d (1978)].

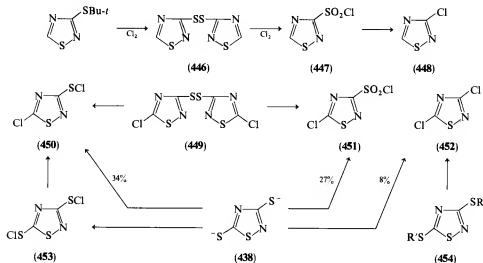
<sup>353</sup> R. Seltzer (to M. & T. Chemicals Inc.), U.S. Patent 3,816,441 (1974) [CA 81, 105,523y (1974)].

<sup>354</sup> W. J. Considine and R. Seltzer (to M. & T. Chemicals Inc.), French Patent 2,001,092 (1969) [CA 72, 56,311f (1970)].

<sup>355</sup> R. Seltzer (to M. & T. Chemicals Inc.), U.S. Patent 3,634,442 (1972) [CA 76, 99,833c (1972)].

<sup>356</sup> E. Söderback, *Justus Liebig's Ann. Chem.* **465**, 184 (1928)].

(454): although the course of this reaction is complex, involving intermediate polythiadiazole disulfides, good yields of pure **452** are obtainable.<sup>147</sup> The alkylthio group in 3-chloro-5-methylthio-1,2,4-thiadiazole is also replaceable by halogen nearly quantitatively upon treatment with chlorine in acetic acid.<sup>357</sup> The pronounced stability of the thiadiazole nucleus in all these chlorolyses is noteworthy.<sup>147</sup>



### 3. Sulfenyl Chlorides and Sulfenamides

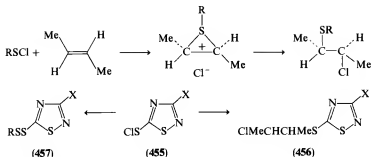
3-Halogeno-1,2,4-thiadiazol-5-yl sulfenyl chlorides (**455**) react rapidly with olefins at  $-40^\circ\text{C}$  to yield adducts (e.g., **456** from butene). The stereospecific mechanism of the exclusive trans addition probably involves episulfonium ions as intermediates. Thus, erythro adducts arise from *trans*-2-butene and threo adducts from *cis*-2-butene; terminal olefins (e.g., isobutylene, 3,3-dimethylbut-1-ene) produce single products, the assigned structures of which (Markovnikov or otherwise) are consistent with their  $^1\text{H}$  NMR spectra.<sup>209</sup>

The 5-sulfenyl chlorides react with thiols<sup>358</sup> or their sodio derivatives,<sup>359</sup> to yield disulfides (**457**) as expected.

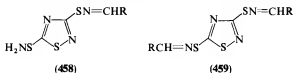
<sup>357</sup> G. L. Smith and D. E. Reese (to Scott & Sons Co.), U.S. Patent 4,081,453 (1978) [CA 89, 43,436b (1978)].

<sup>358</sup> D. E. Ripple (to Lubrizol Corp.), U.S. Patent 3,821,236 (1974) [CA 81, 120,634d (1974)].

<sup>359</sup> H. Juraszyk, H. Wahlig, and W. Hameister (to Merck Patent G.m.b.H.), German Patent 2,556,011 (1977) [CA 87, 117,912m (1977)].



1,2,4-Thiadiazolyl-3,5-sulfenamides form Schiff's bases with aldehydes and ketones. Depending on the conditions, azine formation occurs at the 3 or at both sulfenamide groups, giving **458** or **459**, successively.<sup>360,361</sup> Analogous azines arise from 3-chloro-5-sulfenamido-1,2,4-thiadiazole.<sup>362</sup>



#### 4. Cephalosporins

During recent years, the cephalosporins [**461**, e.g., X = CO(CH<sub>2</sub>)<sub>3</sub>CH(NH<sub>2</sub>)COOH, for cephalosporin C] have commanded a great deal of attention because of their outstanding antibiotic properties: the first realization of this activity, and of the close structural relation of the penicillins (**460**) and cephalosporins (**461**), led to the production and biological screening of large numbers of compounds of this basic pattern. A determined effort to find examples of therapeutic value has met with success: several of the semisynthetic derivatives are now in regular clinical use.<sup>363</sup>

The 3-acetoxymethyl group, and the Δ<sup>2</sup>-unsaturated center of the cephalosporin structure (**461**) are without parallel in penicillin, and the scope of modi-

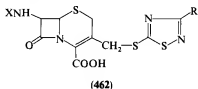
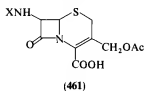
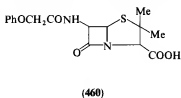
<sup>360</sup> V. A. Ignatov, N. V. Zhorkin, G. A. Blokh, R. A. Akchurina, and L. M. Agafonova, *Zh. Obshch. Khim.* **44**, 2553 (1974).

<sup>361</sup> V. A. Ignatov, G. A. Blokh, Y. S. Rudoi, N. V. Zhorkin, R. A. Akchurina, and L. M. Agafonova, *Izv. Vyssh. Uchebn. Zaved.; Khim. Khim. Tekhnol.* **19**, 290 (1976) [*CA* **85**, 7000p (1976)].

<sup>362</sup> H. Juraszyk, H. Wahlig, and W. Hameister (to Merck Patent G.m.b.H.), German Patent 2,452,618 (1976) [*CA* **85**, 177,426z (1976)].

<sup>363</sup> L. P. Garrod, H. P. Lambert, and F. O'Grady, "Antibiotic and Chemotherapy", 4th ed., p. 88. Churchill-Livingstone, Edinburgh and London, 1973.

lying the former (**461**) is correspondingly greater. In the extensive synthetic programs of recent years, both the 7-acyl group, and the attachment on the 3-methylene side chain of the cephalosporin structure have been systematically varied and the effect on the antimicrobial and pharmacokinetic properties studied. Among the cephalosporins thus synthesized, many examples incorporating a 3-heterylthiomethylene group have been produced. They are obtained ultimately from 7-aminocephalosporanic acid (**461**, X = H) of microbiological origin. At a suitable point in the multistage syntheses, an existing 3-acetoxy group (in **461**) is displaced without difficulty by the direct action of a preformed heteroaromatic thiol in alkali.<sup>363-366</sup> 5-Mercapto-1,2,4-thiadiazoles have been extensively used for this purpose; the resulting compounds (e.g., **462**) have been the subject of nearly 100 patent specifications. Since the claims are all based on the same reaction of known thiadiazoles, they are here merely listed in the briefest possible way for reference.<sup>366</sup>



<sup>364</sup> E. H. Flynn, ed., "Cephalosporins and Penicillins: Chemistry and Biology," pp. 39, 151. Academic Press, New York, 1973.

<sup>365</sup> J. R. E. Hoover and C. H. Nash, "Antibiotics (β-Lactams)" in "Encyclopedia of Chemical Technology" (Kirk-Othmer, ed.), 3rd ed., Vol. 2, pp. 809, Wiley, New York, 1978.

<sup>366</sup> For the reasons given in the text, the following patents are listed as abstract references only: CA 71, 124,458r (1969); 75, 63,804j, 88,625q, 98,582n (1971); 77, 34,587b, 48,487f, 140,109g (1972); 78, 29,792f (1973); 79, 18,733g, 61,983a, 92,244q (1973); 81, 63,645g (1974); 82, 31,344n, 43,444h, 170,989q, 170,993m (1975); 83, 10,109v, 28,252w, 28,257b, 58,844h, 79,266m, 147,488n, 193,348q, 209,412u (1975); 84, 17,386n, 31,104a, 44,102y, 44,103z, 59,518n, 121,860y, 135,698p, 135,699q, 164,812b (1976); 85, 5666m, 21,402c, 33,050z, 46,712s, 46,722v, 108,651g, 192,751v (1976); 86, 5473s, 29,851q, 43,717g, 43,723f, 72,685a, 121,352a, 121,354c, 140,068d, 155,675y, 155,676z, 171,477r, 189,973j, 189,983n (1977); 87, 5993g, 5996k, 39,516u, 68,386g, 68,387h, 85,022c, 102,353f, 102,357k, 135,368t, 201,562e (1977); 88, 22,962j, 37,811h, 37,813k, 50,903j, 89,682m, 105,383x, 121,213x, 121,221y, 190,871x (1978); 89, 24,333z, 146,915m (1978); 90, 23,076b, 38,940c, 87,494u, 103,975j, 121,623x, 137,845g, 146,265v, 186,530e, 186,883b, 204,121h (1979); 91, 20,524f, 20,525g, 20,529m, 57,032v, 211,430g (1979); 92, 41,967p, 163,916s, 181,172a (1980).



Although several of the 3-heterylthiomethylenecephalosporins have shown promise warranting further study, none have so far been adopted in clinical practice.

### E. AMINO-1,2,4-THIA DIAZOLES

The large body of information concerning amino-1,2,4-thiadiazoles<sup>3</sup> has been further augmented, the more reactive 5-amino isomers receiving the major share of the attention. Novel reactions involving intermediates of products having a heteropentalene structure are of special interest. The increasing industrial importance of 1,2,4-thiadiazoles is reflected in the voluminous patent literature dealing with azo dyes derived from 5-amino-1,2,4-thiadiazoles.

#### 1. 5-Amino-1,2,4-thiadiazoles

The 5-amino substituent in 1,2,4-thiadiazoles is acetylated (e.g., by dichloroacetyl chloride) as expected.<sup>367</sup> The combined action of *N,N*-dimethylformamide and phosphorus oxychloride expands it to the dimethylaminomethyleneamino group,<sup>121</sup> and *N,N*-dimethylacetamide and *N*-formylmorpholine react analogously.<sup>368,369</sup> Its conversion to the 5-dimethylsulphimino group ( $-\text{N}=\text{SMe}_2$ ) occurs on treatment with dimethyl sulfoxide in dioxane, in the presence of a tertiary base and a dehydrating agent such as phosphorus oxychloride or methanesulfonyl chloride.<sup>370</sup> 5-Ureido-1,2,4-thiadiazoles are produced by conventional methods from the corresponding amines, either directly,<sup>371-373</sup> or via intermediate *O*-phenylcarbamates,<sup>374</sup> and yield 2,5-dioxoimidazolidines on condensation

<sup>367</sup> C. Metzger, D. Borrmann, R. Wegler, L. Eue, and H. Hack (to Bayer A.G.), South African Patent 68-05643 (1969) [*CA* 72, 79,057s (1970)].

<sup>368</sup> H. Berger, R. Gall, H. Merdes, K. Stach, W. Sauer, and W. Voemel (to Boehringer Mannheim G.m.b.H.), German Patent 2,109,577 (1972) [*CA* 77, 164,657k (1972)].

<sup>369</sup> M. Minagawa and N. Kubota (to Adeka Argus Chemical Co.), Japanese Patent 75/105,559 (1975) [*CA* 84, 45,268u (1976)].

<sup>370</sup> H. Berger, R. Gall, M. Thiel, W. Voemel, and W. Sauer (to Boehringer Mannheim G.m.b.H.), German Patent 2,147,013 (1973) [*CA* 78, 159,647y (1973)].

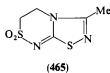
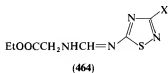
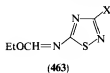
<sup>371</sup> R. R. Schmidt, L. Eue, and C. Metzger (to Bayer A.G.), German Patent 2,407,634 (1975) [*CA* 83, 206,288x (1975)].

<sup>372</sup> A. H. Miller (to Esso Research & Engineering Co.), German Patent 2,037,474 (1971) [*CA* 75, 49,092u (1971)].

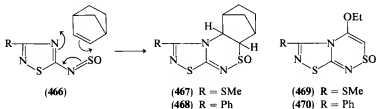
<sup>373</sup> H. Moser and C. Vogel (to Agripat S.A.), German Patent 2,113,033 (1971) [*CA* 76, 31,239h (1972)].

<sup>374</sup> H. Moser and C. Vogel (to Ciba-Geigy Corp.), U.S. Patent 3,822,280 (1974) [*CA* 81, 120,635e (1974)].

with glyoxylic acid monohydrate.<sup>375</sup> Successive treatment of 5-amino-1,2,4-thiadiazoles with triethyl orthoformate and the ethyl ester of glycine yields **463** and **464** (X = 5-nitrofur-2-yl).<sup>376</sup>



Ethenesulfonyl fluoride ( $\text{CH}_2=\text{CH}-\text{SO}_2\text{F}$ ), which functions normally as an excellent fluorosulfonylethylating agent, reacts with  $\alpha$ -amino N-heterocyclics to yield fused 1,2,4-thiadiazine 1,1-dioxides, including the one (**465**) derived from 5-amino-3-methyl-1,2,4-thiadiazole.<sup>377</sup> 3-Substituted 5-amino-1,2,4-thiadiazoles are converted to 5-N-sulfinylamines (**466**) on treatment with 2 moles of thionyl chloride in benzene,<sup>378</sup> or more advantageously, by transsulfinylation using N-sulfinylbenzene sulfonamide.<sup>290</sup> Like other heterocyclic structures bearing this reactive sulfinylamino grouping ortho to the ring nitrogen, they undergo dipolar 1,4-cycloaddition with reactive ethylenes and acetylenes. Their interaction at room temperature with equimolar quantities of bicyclo[2.2.1]hept-2-ene (norbornene), for example, produces the tetracyclic 1,4-methano-1,2,3,4,4a,10a-hexahydro-1,2,4-thiadiazolo[5,4-c]-1,2,4-benzothiadiazine 5-oxides (**467**, **468**, 63–99%). Similarly, their addition to ethoxyacetylene yields 5-ethoxy-1,2,4-thiadiazolo[5,4-c]-1,2,4-thiadiazine 7-oxides (**469**, **470**).<sup>379</sup>



$\alpha$ -Bromoketones attack 5-amino-1,2,4-thiadiazoles at their N4 ring nitrogen, producing the quaternary salts (**471**), from which 5-imino-4-phenacyl- $\Delta^2$ -1,2,4-thiadiazolines (**472**) may be isolated.<sup>380</sup> In appropriate cases the

<sup>375</sup> H. Moser and C. Vogel (to Ciba-Geigy A.G.), German Patent 2,247,266 (1973) [*CA* **78**, 159,609n (1973)].

<sup>376</sup> H. Berger, R. Gall, H. Merdes, K. Stach, W. Sauer, and W. Voemel (to Boehringer Mannheim G.m.b.H.), German Patent 2,153,902 (1973) [*CA* **79**, 42,534p (1973)].

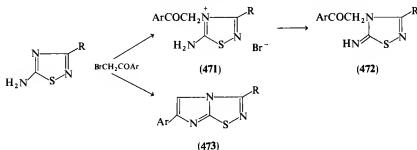
<sup>377</sup> J. J. Krutak, R. D. Burpitt, W. H. Moore, and J. A. Hyatt, *J. Org. Chem.* **44**, 3847 (1979).

<sup>378</sup> A. Michaelis and R. Herz, *Ber. Dtsch. Chem. Ges.* **23**, 3480 (1890).

<sup>379</sup> H. Beecken, *Chem. Ber.* **100**, 2159 (1967).

<sup>380</sup> L. Pentimalli, G. Milani, and F. Biavati, *Gazz. chim. Ital.* **107**, 1 (1977).

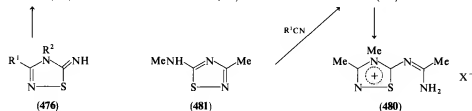
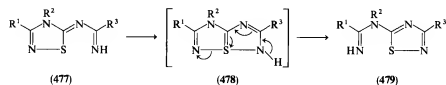
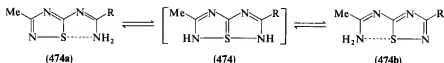
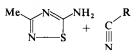
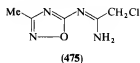
reaction is attended by simultaneous ring closure, resulting in imidazo[1,2-*d*]-1,2,4-thiadiazoles (**473**) directly in one stage. In such examples the quaternary salts (**471**) are not isolable; conversely, if the reaction does terminate at this intermediate stage, the quaternary salt (e.g., **471**, Ar = Ph) cannot be cyclized separately under more stringent conditions. In this sense, the reaction differs from those of 2-aminothiazoles and 2-amino-1,3,4-thiadiazoles, which can be performed in stages without difficulty.<sup>380</sup>



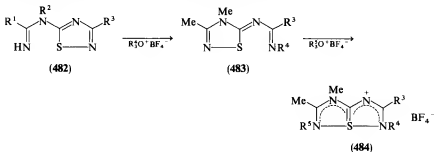
The condensation of 5-amino-3-methyl-1,2,4-thiadiazole with aliphatic or aromatic nitriles yields 1:1-adducts, which are, according to their <sup>1</sup>H NMR spectra, equilibrium mixtures of **474a** and **474b**, the latter predominating by factors ranging from 2 (R = CH<sub>2</sub>Cl) to 50 (R = *p*-ClC<sub>6</sub>H<sub>4</sub>). The ring transformation between the two forms occurs probably by the participation of the  $\pi$ -hypervalent sulfur in **474**, a view that receives further indirect support from the observation that the oxygen analogs occur in one form only (e.g., **475**).<sup>381</sup> The positions of the equilibria between **474a** and **474b** in various solvents and at different temperatures indicate that the sulfur atom in **474** oscillates over a distance of 0.8 Å along the N—S—N axis during ring transformation, at a rate that is slow enough to be detected by NMR spectroscopy, but fast enough to produce integral compounds.<sup>381</sup>

The interaction of 3,4-disubstituted 5-imino- $\Delta^2$ -1,2,4-thiadiazolines (**476**) with acet- or benzimidates [ $R^3C(=NH)OEt$ ] at 60–80°C occurs with loss of ethanol and formation of 1:1-adducts of the reactant and the corresponding nitrile ( $R^3CN$ ). Spectral data suggest, and an X-ray analysis of the prototype (**479**; R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = Me) demonstrated, that the condensation is accompanied by the scission of the original 1,2,4-thiadiazole ring (in **477**) at its S—N bond, and recyclization (to **479**) by a bond switch involving the  $\pi$ -hypervalent sulfur in **478**. The structure (**479**) assigned to the products was further confirmed by their alternative synthesis from authentic **481** and nitriles in the presence of aluminum chloride. Surprisingly, in the formation of salts from **479**, the S—N bond returns to its original location (e.g., **480**).<sup>279</sup>

<sup>381</sup> K. Akiba, T. Kobayashi, and S. Arai, *J. Am. Chem. Soc.* **101**, 5857 (1979).

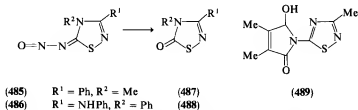


Alkylation of **482** ( $\text{R}^1, \text{R}^2 = \text{Me}$ ) with Meerwein's reagent ( $\text{R}_3\text{O}^+ \text{BF}_4^-$ ) in dichloromethane at  $\sim 40^\circ\text{C}$  is similarly attended by a bond switch, resulting in **483**. A second alkylation step finally yields salts formulated as **484**. An X-ray analysis of the simplest example (**484**;  $\text{R}^3, \text{R}^4, \text{R}^5 = \text{Me}$ ) confirmed it to be 1,2,3,5,6-pentamethyl-1,3,4,6-tetraaza-6a-thia( $S^{\text{IV}}$ ) pentalenium fluoborate, the observed bond lengths reflecting the strong interaction between the linear  $\text{N}-\text{S}-\text{N}$  system.<sup>278</sup> A comparison of the  $^{13}\text{C}$ -NMR



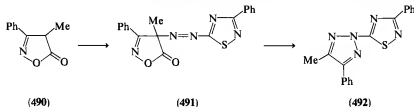
spectra of a series of the salts (484) and of the starting bases (482) as reference compounds has provided numerical values for the  $^{13}\text{C}$  chemical shifts of 484 ( $\text{R}^3, \text{R}^4, \text{R}^5 = \text{Me}$ ), and of 5-(1-iminoethylmethylamino)-3-methyl-1,2,4-thiadiazole (482;  $\text{R}^1, \text{R}^2, \text{R}^3 = \text{Me}$ ). The chemical shifts of all the carbon atoms of the former lie upfield to those of the latter.<sup>382</sup>

Nitrosamines derived from 5-amino-1,2,4-thiadiazoles are readily accessible stable compounds.<sup>3</sup> Thermolysis of the substituted 5-nitrosoimino-1,2,4-thiadiazolines (485<sup>74</sup> and 486<sup>383</sup>) produces the corresponding 5-ketones (487, 488) with evolution of nitrogen almost quantitatively. Their photolysis, involving  $\pi \rightarrow \pi^*$  excitation, proceeds less uniformly. Irradiation of 486 in various solvents yields, as primary products, Hector's base (14b) and phenylcyanamide; subsequent changes produce their 1:1-adduct, as well as 3,5-dianilino-1,2,4-thiadiazole, phenylurea, and other compounds, all in variable moderate yield. The photolytic fragmentation is more complex than that of comparable heterocyclic nitrosimines.<sup>384</sup>



Sodium borohydride reduces *N*-(3-methyl-1,2,4-thiadiazol-5-yl)maleimide to the corresponding hydroxydihydropyrrole (489) without affecting the thiadiazole nucleus.<sup>385</sup>

The interaction of diazotized 5-amino-3-phenyl-1,2,4-thiadiazole and the isoxazolin-5-one (490) in glacial acetic acid at low temperatures produces



<sup>382</sup> K. Akiba, S. Arai, N. Inamoto, K. Yamada, H. Tanaka, and H. Kawazura, *Chem. Lett.*, 1415 (1978).

<sup>383</sup> D. S. Hector, *Ber. Dtsch. Chem. Ges.* **22**, 1176 (1889); **23**, 357 (1890); **25**, 799 (1892).

<sup>384</sup> K. Akiba, T. Tsuchiya, I. Fukawa, and N. Inamoto, *Bull. Chem. Soc. Jpn.* **49**, 550 (1976).

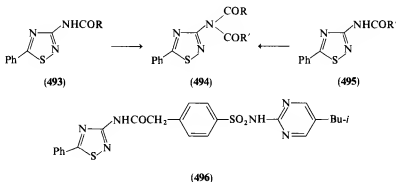
<sup>385</sup> B. Boehner and M. Baumann (to Ciba-Geigy A.G.), German Patent 2,735,841 (1978) [*CA* **88**, 152,415u (1978)]; Ciba-Geigy A.G., French Patent 2,400,013 (1979) [*CA* **92**, 163,836r (1980)].

the stable diazo compound **491**; on treatment with bases this rearranges, with loss of carbon dioxide, to the thiadiazolyl-1,2,3-triazole (**492**).<sup>386</sup>

The extensive patent literature describing the production and application of azo dyes based on amino-1,2,4-thiadiazoles is briefly summarized below under a separate heading.

## 2. 3-Amino-1,2,4-thiadiazoles

3-Amino-1,2,4-thiadiazoles are very weak bases ( $pK_a = 0.8 \pm 0.3$  for **497**,  $R = Et$ ); aqueous solutions of their hydrochlorides are strongly acidic. On being acetylated or sulfonylated, they yield mono- or diacylamino derivatives. In the latter, both acyl groups are located in the 5-amino group, as is demonstrated by the stepwise introduction of two nonidentical acyl residues in cross-over experiments (**493**, **495**  $\rightarrow$  **494**).<sup>182</sup> The amide (**496**) is one of a large number of analogs that were examined for their hypoglycemic properties.<sup>387</sup>



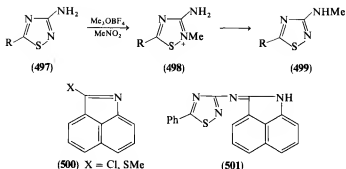
Methylation (of **497**,  $R = Ph$ ) by trimethyloxonium fluoborate produces the 2-quaternary salt (**498**), which isomerizes on basification, probably by a transient  $S-N$  bond cleavage, to 3-methylamino-5-phenyl-1,2,4-thiadiazole (**499**, 95%).<sup>182</sup>

3-Amino-1,2,4-thiadiazoles are diazotized at  $-10^\circ\text{C}$  in phosphoric acid, and couple with naphthol to give moderate yields of diazo dyes.<sup>182,388</sup> In their limited stability, the 3-diazonium salts resemble those of 3-aminoisothiazole, but differ from the more stable 1,2,4-thiadiazole- and isothiazole-5-diazonium salts; a consideration of the  $\pi$ -electron densities leads to the opposite conclusion.<sup>182</sup>

<sup>386</sup> H. Knupfer and C. W. Schellhammer (to Bayer A.G.), German Patent 2,815,956 (1979) [CA 92, 94,406m (1980)].

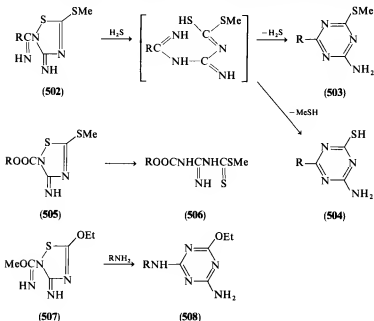
<sup>387</sup> Schering A.G., French Patent 1,599,571 (1970) [CA 74, 87,620b (1971)].

<sup>388</sup> A. Ginsberg and J. Goerdeler, *Chem. Ber.* 94, 2043 (1961).



In its nucleophilic reaction with **500**, 3-amino-5-phenyl-1,2,4-thiadiazole yields derivatives (**501**) that are useful disperse dyes for polyester and acetate fibers.<sup>389</sup>

3-Imino-1,2,4-thiadiazolines provide examples of reductive ring scissions, in which the products are immediately recycled to new heteroring systems. Thus, 2-imidoyl-3-imino-5-methylthio- $\Delta^4$ -1,2,4-thiadiazolines (**502**, see syn-

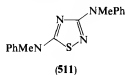
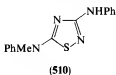
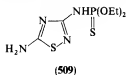


<sup>389</sup> A. Brack, H. Gleinig, R. Raue, and H. Kleiner (to Bayer A.G.), French Patent 1,388,599 (1965) [*CA* **63**, 15,021 (1965)].

theses, type C, Section 2.c) is cleaved by as mild a reducing agent as hydrogen sulfide to yield the two *s*-triazines (**503**, **504**) side by side.<sup>225</sup> The 5-ethoxy analog of **502** yields, with loss of hydrogen sulfide, 2-amino-4-ethoxy-6-phenyl-1,3,5-triazine exclusively (91%).<sup>225</sup> In contrast, scission of the 2-methoxycarbonyl- $\Delta^4$ -1,2,4-thiadiazoline (**505**) with hydrogen sulfide in methanol terminates at the linear guanidine stage (**506**) as expected, there being no scope for recyclization to an *s*-triazine.<sup>229</sup> Conversion of the thiadiazolidine to the *s*-triazine ring system may also occur on hydrolysis,<sup>225</sup> and aminolysis.<sup>228</sup> As an example of the latter reaction, 2-methoxycarbonimidoyl-3-imino-5-ethoxy- $\Delta^4$ -1,2,4-thiadiazoline (**507**) yields principally the substituted *s*-triazines (**508**) by a mechanism that was discussed in detail.<sup>228</sup>

### 3. 3,5-Diamino-1,2,4-thiadiazoles

Acylation of 3,5-diamino-1,2,4-thiadiazole by ethyl chloroformate yields the 3,5-bis(ethoxycarbonylamino) derivative.<sup>67</sup> Phosphorochloridic esters [(RO)<sub>2</sub>POCl] attack the 3-position preferentially, producing the phosphoramidic esters (**509**).<sup>390</sup> The action of diphenylphosphinothioic chloride (Ph<sub>2</sub>PSCl) (see Section IV.C) on Hector's base in pyridine yields a monoacyl derivative, substitution occurring probably at the exocyclic imino group.<sup>391</sup> Methylation of 3,5-bisanilino-1,2,4-thiadiazole with sodium hydride-methyl iodide in dimethylformamide produces the mono and dimethyl derivatives, of structures **510** and **511**, as shown by <sup>15</sup>N and <sup>13</sup>C NMR spectroscopy.<sup>31</sup>

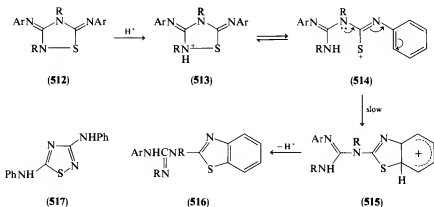


Substituted 3,5-diimino-1,2,4-thiadiazolidines (**512**) are isomerized in acidic media to the corresponding 2-guanidinobenzothiazoles (**516**).<sup>3</sup> Thus 2,4-dimethyl-3,5-bis(phenylimino)-1,2,4-thiadiazole (**512**; R = Me, Ar = Ph) yields **516** (R = Me, Ar = Ph, 82%) on being boiled in 1M hydrochloric acid for 45 min.<sup>48</sup> The tetraphenyl homolog (**512**; R, Ar = Ph) reacts even more rapidly, isomerization being complete within a few minutes.<sup>59</sup> The mechanism shown in Scheme 11 accounts for these results.<sup>59</sup> Protonation at N2 of **512** and fission of the N—S bond generates the cation **514**; electrophilic attack by the sulfur at the phenyl residue (which is activated by the amidino

<sup>390</sup> T. Mukai and S. Sakurai (to Yoshitomi Pharmaceutical Industries Ltd.), Japanese Patent 72/07,369 (1972), [CA 77, 5481g (1972)].

<sup>391</sup> J. Boedeker and R. John-Schenk, Z. Chem. 12, 137 (1972).





SCHEME 11

group) gives the intermediate **515**, which is deprotonated to **516**. When  $R = \text{Me}$ ,  $N_2$  is strongly nucleophilic, and recyclization to **512** is favored; but when  $R = \text{Ph}$ ,  $N_2$  is less nucleophilic, and the formation of **515** predominates. The mechanism is also in accord with the facts that Hector's base (**14b**) and Dost's base (**517**) do not isomerize under these conditions, and that the tetrabenzyl compound (**512**,  $R = \text{Ar} = \text{CH}_2\text{Ph}$ ) is merely cleaved to 1,3-dibenzylurea.<sup>59</sup>

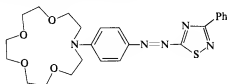
#### 4. Monoazo Dyes from Amino-1,2,4-thiadiazoles

The diazotization of amino-1,2,4-thiadiazoles and the formation of azo dyes from the resulting diazonium salts has been discussed in the original review.<sup>3</sup> The remarkable coupling power of diazotized 5-amino-1,2,4-thiadiazoles had been demonstrated in 1960 by Goerdeler and his co-workers.<sup>392</sup> As was foreshadowed, monoazo dyes incorporating the 1,2,4-thiadiazol-5-ylazo group have proved particularly suitable for dyeing polymers; they impart to polyamide, polyester, and cellulose ester fibers and sheets a range of orange, scarlet, reddish-blue to violet hues, often of a degree of fastness not previously achieved. The technical and economic importance of these dyes is reflected in the voluminous patent literature, which reached its peak in the mid 1970s, and to which many of the leading chemical companies of the major industrial countries contributed.

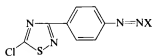
By far the greatest number of monoazo dyes of this type are based on diazotized 5-amino-3-phenyl-1,2,4-thiadiazole. A great variety of examples, their structure and properties modulated by a suitable choice of "couplers" are the subject of numerous, often very substantial<sup>392a</sup> patent specifications.<sup>393-424</sup> An example of more than ordinary interest is (3-phenyl-1,2,4-thiadiazol-5-yl)-[4-(4,7,10,13-tetraoxa-1-azacyclopentadecyl)phenyl] diazen

- <sup>392</sup> J. Goerdeler, H. Haubrich, and J. Galinke, *Chem. Ber.* **93**, 397 (1960).
- <sup>392a</sup> The length of many of the German patent specifications approaches or exceeds 100 pages.
- <sup>393</sup> H. Wunderlich and K. Weis, French Patent 1,361,299 (1964) [CA **62**, 5366 (1965)]; Belgian Patent 640,973 (1964) [CA **62**, 13,279 (1965)]; German Patent 1,218,091 (1966) [CA **65**, 13,851 (1966)].
- <sup>394</sup> Farbenfabriken Bayer A.G., Netherlands Patents Appl. 6,400,137 (1964); 6,403,568 (1965) [CA **62**, 1787 (1965); **64**, 3736 (1966)].
- <sup>395</sup> Ciba Ltd., Netherlands Patents Appl. 6,514,608 (1966); 6,600,581 (1966) [CA **65**, 12,314 (1966); **66**, 18,852t (1967)].
- <sup>396</sup> G. Wolfrum, W. Knobloch, and H. Gold (to Bayer A.G.), British Patent 1,117,588 (1968) [CA **69**, 87,965q (1968)].
- <sup>397</sup> Ciba Ltd., British Patent 1,147,546 (1969) [CA **71**, 71,915d (1969)].
- <sup>398</sup> V. Ramanathan (to Ciba Ltd.), German Patents 1,919,081, 1,922,901 (1969) [CA **72**, 122,903d (1970); **73**, 16,267k (1970)]; Swiss Patent 517,145 (1972) [CA **77**, 36,371a (1972)].
- <sup>399</sup> P. Suchanek and C. Taube (to Bayer A.G.), German Patent 1,941,701 (1971) [CA **74**, 127,537p (1971)].
- <sup>400</sup> K. L. Moritz and R. Neeff (to Bayer A.G.), German Patent 2,004,131 (1971) [CA **75**, 130,765n (1971)].
- <sup>401</sup> J. L. Leng and C. Morris (to ICI Ltd.), British Patent 1,247,683 (1971) [CA **76**, 60,925j (1972)].
- <sup>402</sup> G. Cseh and W. Mueller (to Ciba-Geigy A.G.), German Patent 2,128,529 (1971) [CA **76**, 128,790u (1972)].
- <sup>403</sup> W. Kruckenberg (to Bayer A.G.), German Patents 2,036,997, 2,042,662, 2,059,947 (1972); 2,065,685 (1975) [CA **77**, 7283t, 36,373c, 153,903m (1972); **83**, 195,205q (1975)].
- <sup>404</sup> R. Entschel and B. Henzi (to Sandoz Ltd.), German Patent 2,228,792 (1972) [CA **78**, 85,917n (1973); B. Henzi (to Sandoz Ltd.), German Patent 2,338,729 (1974) [CA **81**, 65,190d (1974)]; Swiss Patent 508,709 (1971) [CA **76**, 73,735x (1972)].
- <sup>405</sup> Ciba-Geigy A.G., French Patent 2,091,588 (1972) [CA **77**, 128,064f (1972)].
- <sup>406</sup> V. Ramanathan (to Ciba-Geigy A.G.), German Patent 2,221,364 (1972) [CA **78**, 125,819r (1973)].
- <sup>407</sup> N. B. Desai (to Ciba-Geigy A.G.), German Patents 2,256,313-4 (1973) [CA **79**, 54,860e, 54,862g (1973)].
- <sup>408</sup> V. Ramanathan (to Ciba-Geigy A.G.), German Patents 2,263,007, 2,263,109 (1973); 2,429,927 (1975) [CA **79**, 106,123 (1973); **80**, 4894u (1974); **82**, 172,589h (1975)]; U.S. Patent 4,066,637 (1978) [CA **88**, 122,664g (1978)].
- <sup>409</sup> S. Fujimo, H. Honda, and T. Hattori (to Mitsubishi Chemical Industries Co.), Japanese Patent 23,823 (1974) [CA **81**, 154,525j (1974)].
- <sup>410</sup> P. W. Barker, V. Boyd, B. R. Fishwick, and A. Quayle (to ICI Ltd.), German Patent 2,412,108 (1974) [CA **82**, 32,446j (1975)].
- <sup>411</sup> G. Boehmke (to Bayer A.G.), German Patent 2,309,528 (1974) [CA **82**, 87,663h (1975)].
- <sup>412</sup> W. Kruckenberg (to Bayer A.G.), German Patents 2,320,361 (1974), 2,508,884 (1976) [CA **82**, 141,597e (1975); **85**, 161,875j (1976)].
- <sup>413</sup> V. Ramanathan (to Ciba-Geigy A.G.), U.S. Patents 3,954,398 (1976), 4,083,688 (1978) [CA **85**, 79,675k (1976); **89**, 112,341f (1978)]; Swiss Patent 576,509 (1976) [CA **85**, 79,684n (1976)].
- <sup>414</sup> V. Ramanathan, U. Schlesinger, and R. DeMontmollin (to Ciba-Geigy A.G.), German Patent 2,554,639 (1976) [CA **85**, 79,680h (1976)].
- <sup>415</sup> W. Lang and G. Hegar (to Ciba-Geigy A.G.), German Patent 2,549,436 (1976) [CA **85**, 34,639k (1976)].

(518), which was synthesized in the course of a wider study of ion-selective crown-ether dyes, for complexing with cations, so as to influence the ground and excited states of the chromophore differentially. The compound is obtained as a red crystallizable solid from 3-phenyl-1,2,4-thiadiazole-5-nitrosamine in 70% yield.<sup>425</sup>



(518)



(519)

Other examples of monoazo dyes of the general type have been produced from diazotized 3-alkylmercapto-,<sup>114,115,401,426-430</sup> 3-alkylsulfonyl-,<sup>114,115,</sup>

#### Footnotes for 416-430

- <sup>416</sup> G. Hegar (to Ciba-Geigy A.G.), Swiss Patent 579,125 (1976) [*CA* **85**, 144,702h (1976)].  
<sup>417</sup> E. Schleusener (to Sandoz Patent G.m.b.H.), German Patent 2,604,571 (1976) [*CA* **85**, 144,700f (1976); Swiss Patent 595,420 (1978) [*CA* **88**, 192,745h (1978)].  
<sup>418</sup> V.P. Kubba (to Ciba-Geigy A.G.), German Patent 2,607,269 (1976) [*CA* **85**, 194,078e (1976); India Patent 145,910 (1979) [*CA* **92**, 165,207k (1980)].  
<sup>419</sup> P. Jayaraman (to Ciba-Geigy A.G.), German Patent 2,613,595 (1976) [*CA* **86**, 44,750z (1977)]; India Patent 145,919 (1979) [*CA* **92**, 165,206j (1980)].  
<sup>420</sup> S. Koller, R. Zink, and H. Schwander (to Ciba-Geigy A.G.), German Patent 2,632,203 (1977) [*CA* **86**, 157,017j (1977)].  
<sup>421</sup> W. Groebke and R. Wirz (to Sandoz A.G.), Swiss Patent 589,697 (1977) [*CA* **87**, 119,240q (1977)].  
<sup>422</sup> G. Hegar and H. J. Angliker (to Ciba Geigy A.G.), U.S. Patent 4,028,323 (1977) [*CA* **87**, 137,304t (1977)].  
<sup>423</sup> Ciba-Geigy A.G., Swiss Patent 606,297 (1978) [*CA* **90**, 73,296u (1979)].  
<sup>424</sup> P. Koppitz and E. Siegel (to Bayer A.G.), German Patent 2,702,627 (1978) [*CA* **89**, 164,930s (1978)].  
<sup>425</sup> J. P. Dix and F. Voegtli, *Chem. Ber.* **113**, 457 (1980).  
<sup>426</sup> E. Hahn and H. G. Wippel (to BASF A.G.), French Patent 1,504,896 (1967) [*CA* **70**, 20,981u (1969)]; U.S. Patent 3,642,767 (1972) [*CA* **77**, 128,054c (1972)].  
<sup>427</sup> M. A. Weaver, H. S. Pridden, and C. A. Coates (to Eastman Kodak Co.), U.S. Patents 3,660,374 (1972), 3,816,388 (1974) [*CA* **77**, 76,663d (1972); **83**, 61,644y (1975)].  
<sup>428</sup> N. Grund, G. Hansen, H. Kaak, and W. D. Kermer (to BASF A.G.), German Patents 2,751,337, 2,752,805, 2,817,201 (1979) [*CA* **91**, 75,708z, 75,709a (1979); **92**, 78,093b (1980)].  
<sup>429</sup> D. R. Waring (to Kodak Ltd.), British Patent 1,506,155 (1978) [*CA* **89**, 164,926v (1978)].  
<sup>430</sup> G. Seybold, H. Eilingsfeld, and G. Hansen (to BASF A.G.), German Patent 2,738,885 (1979) [*CA* **91**, 6397k (1979)].

<sup>401,427</sup> 3-chloro-,<sup>431</sup> 3-trichloromethyl-,<sup>432</sup> and a number of other 3-substituted 5-amino-1,2,4-thiadiazoles,<sup>118,433-437</sup> as well as the parent 5-amine.<sup>438</sup> Useful dye properties are possessed by azo compounds, in which the thiadiazole nucleus is remote from the diazo group (e.g., **519**).<sup>439</sup>

Conditions have been specified for incorporating such dyes in polyurethanes,<sup>440</sup> polyamides, and polyesters,<sup>441</sup> and methods have been developed for using them in color printing on polymer fabrics.<sup>429</sup> Processes are available for imparting to the dyes a physical form especially favorable for their dyeing function.<sup>442</sup> A physicochemical study of the influence of the structure of azo dyes on the ease, with which their molecules align with the orientation direction of the liquid crystalline host, has included an example incorporating a 1,2,4-thiadiazole moiety.<sup>443</sup> In an investigation, prompted by a serious accident, of the stability and potential explosive properties of a range of diazotized amines used on an industrial scale, 5-amino-3-(4'-pyridyl)-1,2,4-thiadiazole was found to be among the safest compounds tested.<sup>444</sup>

### 5. Other 1,2,4-Thiadiazole Dyes

In addition to the foregoing monoazo dyes, other structures incorporating 1,2,4-thiadiazole residues possess useful dyeing properties. Examples are

<sup>431</sup> V. Ramanathan (to Ciba Ltd.), German Patent 2,006,131 (1970) [*CA* **74**, 4640j (1971)].

<sup>432</sup> J. C. Petitpierre and V. Ramanathan (to Ciba-Geigy A.G.), German Patent 2,460,238 (1975) [*CA* **84**, 152,201p (1976)].

<sup>433</sup> Badische Anilin und Soda Fabrik A.G., French Patent 2,010,017 (1970) [*CA* **73**, 99,998y (1970)].

<sup>434</sup> E. Hahn and H. G. Wippel (to BASF A.G.), U.S. Patent 3,621,007 (1971) [*CA* **76**, 87,151r (1972)].

<sup>435</sup> P. Moser and V. Ramanathan, German Patent 2,147,809 (1972) [*CA* **77**, 90,037j (1972)].

<sup>436</sup> J. Dehnert and G. Lamm (to BASF A.G.), German Patent 2,259,103 (1974) [*CA* **83**, 12,159k (1975)].

<sup>437</sup> K. Leverenz (to Bayer A.G.), German Patent 2,733,757 (1979) [*CA* **90**, 170,156f (1979)].

<sup>438</sup> H. J. Angliker, U. Krueger, R. Portmann, A. C. Rochat, and W. Weiskat (to Ciba-Geigy A.G.), German Patent 2,509,560 (1975) [*CA* **84**, 46,041b (1976)].

<sup>439</sup> Badische Anilin und Soda Fabrik A.G., Netherlands Patent Appl. 6,513,932 (1966) [*CA* **65**, 10,703 (1966)].

<sup>440</sup> K. Nonn, R. Hoernle, J. Koerner, and R. Schliebs (to Bayer A.G.), German Patent 1,900,759 (1970) [*CA* **73**, 99,591k (1970)].

<sup>441</sup> W. Kruckenberg and K. H. Schuendehuetten (to Bayer A.G.), German Patent 2,724,951 (1978) [*CA* **90**, 188,450g (1979)].

<sup>442</sup> R. Hoernle, H. J. Reppert, H. H. Moells, and W. Gohrbandt (to Bayer A.G.), German Patents 1,770,931-2 (1972) [*CA* **86**, 18,354d-5e (1977)].

<sup>443</sup> A. Bloom and P. L. K. Hung, *Mol. Cryst. Liq. Cryst.* **40**, 213 (1977).

<sup>444</sup> P. Bersier, L. Valpiana, and H. Zubler, *Chem.-Ing.-Tech.* **43** 1311 (1971).

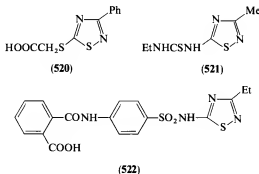
derived from naphthalene,<sup>445</sup> coumarin,<sup>446</sup> isoindolinone,<sup>447</sup> and anthraquinone.<sup>448</sup>

## V. Biological Properties

The remarkable pesticidal properties of 1,2,4-thiadiazole derivatives, especially of organophosphorus compounds, and of 5-ethoxy-3-trichloromethyl-1,2,4-thiadiazole and its analogs are the subject of brief separate Sections. Screening programs and individual studies continue<sup>3</sup> to reveal a variety of other biological activities of 1,2,4-thiadiazoles.

A wide range of 1,2,4-thiadiazoles has been deliberately synthesized in the search for *herbicides*, and success is frequently claimed in the patent literature. Favorable data are reported for fluorinated structures, e.g., 1-(3-trifluoromethyl-1,2,4-thiadiazol-5-yl)-3,3-dimethylurea.<sup>373</sup>

3-Phenyl-5-carboxymethylthio-1,2,4-thiadiazole ("NC 9634") (520) has *plant-growth regulating* properties, inhibiting lateral budding in the grape vine (*vitis vinifera*),<sup>449</sup> but inducing branching in certain varieties of apple trees.<sup>450</sup> Treatment of cotton with this compound, or its salts, esters, or



<sup>445</sup> H. Schwander and C. Zickendraht (to Ciba-Geigy A.G.), German Patent 2,724,541 (1977) [CA 88, 106,761f (1978)].

<sup>446</sup> H. Scheuermann, D. Augart, and W. Mach (to BASF A.G.), German Patent 2,226,211 (1973) [CA 82, 87,681n (1975)].

<sup>447</sup> C. Frey and J. Von der Crone (to Ciba-Geigy A.G.), German Patent 2,546,038 (1976) [CA 85, 34,645j (1976)].

<sup>448</sup> W. Ball and E. Hahn (to BASF A.G.), Belgian Patent 660,635 (1965) [CA 64, 9854 (1966)].

<sup>449</sup> S. Lavee, A. Erez, and Y. Shulman, *Vitis* 16, 89 (1977) [CA 87, 195,322h (1977)].

<sup>450</sup> H. Plich and E. S. Hegazi, *Fruit Sci Rep.* 4, 11 (1977); H. Plich and A. Basak, *ibid.* 5, 23 (1978) [CA 88, 17,196h (1978); 91, 1307w (1979)].

amides, increases yields appreciably.<sup>451</sup> It has been found to reduce the transpiration rate, and to increase the loss of foliar nitrogen, in the soybean<sup>452</sup> and to inhibit polar auxin transport in tobacco stem segments.<sup>453</sup>

5-Thioureido-1,2,4-thiadiazoles (e.g., **521**) are *virucides*, being especially active against Tobacco mosaic virus.<sup>454</sup> Quantitative data are available concerning the *bacteriostatic*<sup>455</sup> and *fungistatic* properties<sup>456</sup> of selected 1,2,4-thiadiazoles. 5-(*N*<sup>4</sup>-Phthaloyl)sulfanilamido-3-ethyl-1,2,4-thiadiazole (**522**) is claimed to be especially suitable in the treatment of infectious intestinal diseases, because it is only slowly absorbed from the gastrointestinal tract.<sup>457</sup> A single dose of 5-ethoxy-3-trichloromethyl-1,2,4-thiadiazole (100 mg/kg i.p.) prolongs the pentobarbital sleeping time (in mice), indicating that it inhibits the detoxification of this drug in the liver.<sup>458</sup>

Reports are available of the screening of 1,2,4-thiadiazoles<sup>459,460</sup> as systemic *insecticides*. 5-Alkoxy-3-trichloromethyl-1,2,4-thiadiazoles, the proved fungicides, have also insecticidal and acaricidal properties.<sup>461</sup> 1,2,4-Thiadiazoles may act as *chemosterilants*<sup>462</sup>: 5-amino-3-methyl(or methylthio)-1,2,4-thiadiazole are found to have this action in the housefly.<sup>463,464</sup> 5-Chloro-3-ethylthio-1,2,4-thiadiazole has nematocidal activity.<sup>465</sup>

<sup>451</sup> S. D. Hoogstraaten (to Fisons Ltd.), U.S. Patent 4,092,149 (1978) [CA **89**, 158,765a (1978)].

<sup>452</sup> R. T. Weiland and C. A. Stutte, *Proc. Plant Growth Regul. Work. Group* **5**, 78 (1978) [CA **90**, 49,532x (1979)].

<sup>453</sup> P. H. Rubery, *Plant Sci. Lett.* **14**, 365 (1979) [CA **91**, 33,996 (1979)].

<sup>454</sup> T. Noguchi, T. Hosotsuji, Y. Yasuda, and S. Kano (to Nippon Soda Co.), Japanese Patent 38,146 (1973) [CA **81**, 73,389r (1974)].

<sup>455</sup> W. Weuffen, T. Pyl, W. Gruebner, and W. D. Juelich, *Pharmazie* **20**, 629 (1965).

<sup>456</sup> G. Tartler and W. Weuffen, *Pharmazie* **21**, 425 (1966).

<sup>457</sup> H. Horstmann, K. G. Metzger, and U. Woerffel (to Bayer A.G.), British Patent 1,083,607 (1967) [CA **68**, 95,805g (1968)].

<sup>458</sup> R. R. Dalvi and C. D. Howell, *Bull. Environ. Contam. Toxicol.* **17**, 225 (1977) [CA **86**, 184,232g (1977)].

<sup>459</sup> R. O. Drummond, *U.S. Agric. Res. Serv. [Rep.]* (1976) **ARS-S-101** [CA **84**, 144,812y (1976)].

<sup>460</sup> A. B. DeMilo, D. M. Ostromecky, S. C. Chang, R. E. Redfern, and R. L. Fye, *J. Agric. Food Chem.* **26**, 164 (1978).

<sup>461</sup> T. O. Evrard (to Olin Corp.), U.S. Patent 4,057,639 (1977) [CA **88**, 59,437t (1978)].

<sup>462</sup> J. W. Haynes, E. Mattix, N. Mitlin, A. B. Borkovec, and O. H. Lindig, *U.S. Agric. Res. Serv. [Rep.]* (1976) **ARS-S-131** [CA **86**, 151,443y (1977)].

<sup>463</sup> A. B. DeMilo, R. L. Fye, and A. B. Borkovec, *J. Econ. Entomol.* **66**, 1007 (1973).

<sup>464</sup> R. L. Fye and J. E. Oliver, *J. Agric. Food Chem.* **22**, 374 (1974).

<sup>465</sup> T. Toyama, A. Kojima, T. Katayama, O. Morikawa, and S. Ogawa (to Mitsui Toatsu Chemical Co.), Japanese Patent 30,833 (1972) [CA **78**, 155,430z (1973)].

3,5-Diamino-1,2,4-thiadiazole possesses *radioprotective activity*<sup>3</sup>; a correlation has been established<sup>466</sup> between this property and a depressive effect on thymidine uptake on myelocytes, and on the rate of DNA synthesis in bone marrow and intestinal epithelium. The radioprotective activity of 5-amino-3-methylthio-1,2,4-thiadiazole has also been reported.<sup>467</sup>

Only few biochemical investigations have been concerned with 1,2,4-thiadiazoles. In a comparative study involving a large number of chemotherapeutic agents, the protein binding of 1,2,4-thiadiazoles in blood serum has been measured.<sup>468</sup> A number of derivatives have been tested for their power to inhibit electron transport and phosphorylation; of these, 3-isopropyl-5-(3,4-dichlorophenylamino)-1,2,4-thiadiazole was the most active.<sup>469</sup> Thiadiazole oximes, in common with other oximes, reactivate organophosphate-inhibited acetylcholinesterase, but are of limited prophylactic value against organophosphorus poisoning.<sup>470</sup>

### 5-ETHOXY-3-TRICHLOROMETHYL-1,2,4-THIA DIAZOLE AS A PESTICIDE

The preparation of 5-ethoxy-3-trichloromethyl-1,2,4-thiadiazole was first reported<sup>3,471</sup> in 1962, and its excellent pesticidal properties publicized shortly afterwards.<sup>472</sup> Since then its effectiveness and usefulness as a systemic soil fungicide have been proved in a large number of trials. It has become firmly established in agricultural practice, and is known under a variety of commercial names,<sup>473,474</sup> Terrazole being the most common. Numerous

<sup>466</sup> H. A. B. Simons and E. M. Davis, *Int. J. Radiat. Biol.* **10**, 343 (1966).

<sup>467</sup> G. N. Krutovskikh, A. M. Rusanov, G. F. Gornaeva, L. P. Vartanyan, and M. B. Kolesova, *Khim.-Farm. Zh.* **11**, 48 (1977).

<sup>468</sup> W. Scholtan, *Int. Congr. Chemother., Proc.*, **3rd.**, 1963, 251 (1964) [*CA* **64**, 1191 (1966)].

<sup>469</sup> P. Bracha, M. Luwisch, and N. Shavit, *Pestic. Chem., Proc. Int. IUPAC Congr. Pestic. Chem.*, **2nd.**, 1971, Vol 5, 141 (1972) [*CA* **80**, 23,463u (1974)].

<sup>470</sup> H. P. Benschop, L. R. A. DeJong, J. A. J. Vink, H. Kienhuis, F. Berends, D. M. W. Elskamp, L. A. Kepner, E. Meeter and R. P. L. S. Visser, *Med. Prot. Chem.-Warf. Agents (Pap. Symp.)*, 1974, 120 (1976) [*CA* **86**, 26, 689g (1977)].

<sup>471</sup> H. Schroeder, R. F. W. Raetz, W. Schnabel, H. Ulrich, E. Kober, and C. Grundmann, *J. Org. Chem.* **27**, 2589 (1962).

<sup>472</sup> H. Schroeder and J. H. Reinhart, Belgian Patent 624,636 [*CA* **59**, 11,508 (1963)]; Olin Mathieson Chemical Corp., French Patent 1,339,238 (1963) [*CA* **60**, 5513 (1964)].

<sup>473</sup> 5-Ethoxy-3-trichloromethyl-1,2,4-thiadiazole (Registry No. 2593-15-9) appears in the Literature under the following names: OM-2424, Terrazole, Truban, ETMT, Terracoat L 21, Koban, Aaterra, Etridiazole, Ethazole, Pansoil (Japan), Echlomezole (Japan).

<sup>474</sup> Mixtures of 5-ethoxy-3-trichloromethyl-1,2,4-thiadiazole and pentachloronitrobenzene (Registry No. 8065-61-0) are named Terracoat, Terrachlor-Super X. Other mixtures have been used less frequently.

reports have described the protection afforded by this compound, either alone<sup>475</sup> or in admixture with other fungicides,<sup>476</sup> to a wide range of plants and crops (including cereals, rice, cotton, tobacco, potato, tomato, apple, and other fruits), and have compared it favorably with other well-known pesticides. The 5-substituent in the structure may be varied, with retention of the fungicidal properties.<sup>477</sup>

In addition to extensive empirical laboratory and field trials<sup>475,476</sup> designed to establish suitable conditions for its effective use, the biochemical and biological properties of Terrazole are being studied, with the ultimate aim of elucidating its mode of action.

By employing <sup>14</sup>C-labeled Terrazole, its distribution in various parts of plants, including seeds, has been investigated.<sup>478</sup> Information is available about the rate of its uptake by cell suspensions.<sup>479</sup>

Experiments carried out with *Mucor mucedo* (mildew) show that Terrazole inhibits, at the cellular level, the synthesis of triglycerides and sterol esters, stimulates that of free fatty acids and phospholipids,<sup>480</sup> but does not appreciably affect nucleic acid synthesis.<sup>481</sup> Phospholipase is released in cell membranes and mitochondria; the associated reduction in mitochondrial

<sup>475</sup> The citations in this and the following reference list report tests describing pesticidal effects of Terrazole. Because of their large number and only marginal chemical interest, they are given as abstract references only: *CA* **61**, 6302 (1964); **62**, 5822 (1965); **64**, 4195; **65**, 11270 (1966); **69**, 51,178w, 66,399t (1968); **70**, 19,209s, 67,080q, 76,703x, **71**, 111,811a (1969); **72**, 77,793e; **73**, 2913f, 2914g, 2926n, 13379n, 24,189b (1970); **74**, 50,622c, 110,769t; **75**, 19128t, 109,084e (1971); **76**, 42,592u, 122,758t, 122,761p; **77**, 1661t, 1807v, 148,349f (1972); **78**, 80,712g; **79**, 1214r, 112,268f (1973); **80**, 104,739r; **81**, 100,526s, 164,526z (1974); **82**, 81,564e, 165,729a, 165,884x; **83**, 2261y, 23,327q, 73,247j (1975); **84**, 100,697k, 116,766t, 131,300e; **85**, 15,113t, 42,011q, 105,172r, 172,567m (1976); **87**, 178,789y, 178,834j (1977); **88**, 33,005a, 46,172c, 46,177h, 116,200m, 131,769x, 131,826p; **89**, 37,913p, 71,925d, 174,905b, 210,284j (1978); **90**, 1553c, 34,828z, 81,937u, 198,729u, 198,730n; **91**, 1220n, 50,946n, 85,248p, 135,399m, 169,785z, 169,786a (1979); **92**, 53,243n, 105,652s, 105,660t, 141,629y (1980).

<sup>476</sup> Terrazole—PCNB (pentachloronitrobenzene) is the mixture most frequently tested: *CA* **70**, 10,541m (1969); **73**, 76,086k, 119,574n (1970); **74**, 139,948m (1971); **77**, 1638r, 44,163z, 84,172h (1972); **78**, 53,917w, 80,710e, 106,870j; **79**, 39,214d (1973); **80**, 23,425h, 104,728m; **81**, 34,365k (1974); **82**, 52,508j, 150,334u, 150,336w; **83**, 142,918t (1975); **85**, 29,378v, 73,345f (1976); **86**, 823w, 184,395n; **87**, 195,271r (1977); **88**, 1383f, 17,252y, 184,451u; **89**, 101,609y (1978); **91**, 50,947p, 50,969x, 69,824u, 84,919w, 118,494w (1979); **92**, 123,212c, 175,619k, 141,628x (1980).

<sup>477</sup> E. Smith, U.S. Patent 3,884,929 (1975) [*CA* **83**, 131,608r (1975)].

<sup>478</sup> N. R. O'Neill, G. C. Papavizas, and J. A. Lewis, *Phytopathology* **69**, 690 (1979) [*CA* **91**, 169,788c (1979)].

<sup>479</sup> G. Josepovits, *Proc. Hung. Annu. Meet. Biochem.* **19** 83 (1979) [*CA* **92**, 17,157d (1980)].

<sup>480</sup> H. Lyr, B. Laussmann, and G. Casperson, *Z. Allg. Mikrobiol.* **15**, 345 (1975).

<sup>481</sup> G. Casperson and H. Lyr, *Z. Allg. Mikrobiol.* **15**, 481 (1975).



function may be responsible for or contribute to the fungostatic effect.<sup>482</sup> There is a correlation between growth inhibition and the respiration rate in certain species of fungi (*Pythium*): the oxidation rate of glucose and acetate are unaffected, but that of succinate and malate are retarded. The evidence is consistent with the occurrence of a block in the electron transport system, possibly between cytochrome *b* and *c*.<sup>483</sup>

Other enzyme studies (employing species of *Pythium*) have shown that Terrazole decreases the activity of exocellulase, increases that of endocellulase, and is substantially without effect on that of polygalacturonase and pectin methyl esterase.<sup>484</sup> It partially inhibits the incorporation of uridine diphosphateacetylglucosamine into chitin in the presence of chitin synthetase, *in vitro*.<sup>485</sup>

Terrazole has also an inhibiting effect on microorganisms active in the nitrification process (i.e., the conversion of ammonium salts to nitrates) in soil.<sup>486-488</sup> However, under field conditions, the inhibition of nitrification is of limited duration; pasture yields, for example, are not increased.<sup>489</sup> 3-Trichloromethyl-1,2,4-thiadiazole-5-amines exhibit the same properties.<sup>490</sup>

The toxicity of Terrazole to mammals<sup>491</sup> and freshwater animals<sup>492</sup> has been determined. Below specified concentrations, the compound is not phytotoxic to a representative selection of plants.<sup>493</sup> Its persistence in the soil

<sup>482</sup> H. Lyr, G. Caspersen, and B. Laussmann, *Z. Allg. Mikrobiol.* **17**, 117 (1977); B. Radzuhn and G. Caspersen, *Abh. Akad. Wiss. DDR, Abt. Math., Naturwiss. Tech.*, 195 (1979) [CA **92**, 123,228n (1980)].

<sup>483</sup> P. Halos and O. C. Huisman, *Phytopathology* **66**, 152, 158 (1976) [CA **84**, 131,302g-3h (1976)].

<sup>484</sup> B. G. Desai, M. Geypens and C. Van Assche, *Meded. Fac. Landbouwwet., Rijksuniv. Gent* **38**, 1455 (1973) [CA **81**, 86,638w (1974)].

<sup>485</sup> H. Lyr and W. Seyd, *Z. Allg. Mikrobiol.* **18**, 721 (1978); *Abh. Akad. Wiss. DDR, Abt. Math., Naturwiss. Tech.*, 151 (1979) [CA **92**, 123,226k (1980)].

<sup>486</sup> K. Sommer, *Landwirtsch. Forsch.* **25**, 22 (1970); **27**, 64, 74 (1972); **31**, 291 (1978) [CA **74**, 110,863u (1971); **78**, 3262h, 3261g (1973); **90**, 5072t (1979)].

<sup>487</sup> D. W. Nelson, L. E. Sommers, D. M. Huber, and H. L. Warren, *Agric. Energy [Proc. Conf.]*, 1976, 361-76 (1977) [CA **89**, 5281q (1978)].

<sup>488</sup> F. T. Turner, *Soil Sci. Soc. Am. J.* **43**, 955 (1979) [CA **92**, 21,358n (1980)].

<sup>489</sup> M. A. Turner and A. N. Macgregor, *N. Z. J. Agric. Res.* **21**, 39 (1978) [CA **89**, 74,888e (1978)].

<sup>490</sup> M. Okutsu, O. Wakabayashi, T. Shibata, S. Fujita, and M. Tsuda (to Mitsubishi Chemical Industries Co.), Japanese Patent 4,964 (1972) [CA **78**, 70,742c (1973)].

<sup>491</sup> J. F. Borzelleca, P. S. Larson, E. M. Crawford, G. R. Hennigar, E. J. Kuchar and H. H. Klein, *Toxicol. Appl. Pharmacol.* **18**, 522 (1971) [CA **74**, 123,982g (1971)].

<sup>492</sup> Y. Nishiuchi and K. Yoshida, *Noyaku Kensasho Hokoku* **14**, 66 (1974); **16**, 65 (1976) [CA **83**, 142,689u (1975); **90**, 34,654q (1979)]; Y. Nishiuchi and K. Asano, *Suisan Zoshoku* **25**, 151 (1978); **27**, 48, 119 (1979) [CA **89**, 71814s (1978); **92**, 70,678a, 88,958b (1980)].

<sup>493</sup> H. N. Miller and R. T. DeNeve, *Plant Dis. Rep.* **55**, 587 (1971) [CA **76**, 772x (1972)].

when applied as fungicide has been measured,<sup>494</sup> and residue data<sup>495</sup> are available. A tolerance of 0.15 ppm is established by law for the combined residues of Terrazole and its metabolite, the 3-carboxylic acid, on certain fruits.<sup>496</sup>

A short review, without references, discussing the properties, mechanism of action, and methods of applying Terrazole has appeared in the Japanese language.<sup>497</sup>

1,2,4-Thiadiazoles other than Terrazole have also been found to possess significant fungicidal activity. They are generally derivatives incorporating both halogeno and sulfur functions and include compounds such as bis(3-halogeno-1,2,4-thiadiazol-5-yl) disulfides,<sup>498</sup> 3-chloro-1,2,4-thiadiazol-5-yl phenyl disulfide,<sup>499</sup> 3-chloro-5-phenylsulfonylthio-1,2,4-thiadiazole and analogs,<sup>500</sup> as well as other 5-sulfonyl and sulfinyl derivatives,<sup>501</sup> and 2-(3-methyl-1,2,4-thiadiazol-5-yl)thio-5-trifluoromethyl-1,3,4-thiadiazole.<sup>502</sup> Fungicidal properties are also shown by relatively simpler structures such as 3-amino-5-chloro-1,2,4-thiadiazole<sup>503</sup> and 3-phenyl-1,2,4-thiadiazol-5-ylthioacetic acid,<sup>504</sup> and by condensed structures such as the thiadiazolo-benzimidazole (523).<sup>505</sup>

Like Terrazole, 3,5-diamino-1,2,4-thiadiazole acts as an effective inhibitor of the oxidation of ammonium salts to nitrates in soil.<sup>506</sup>

<sup>494</sup> G. J. Muller, M. B. Linn, and J. B. Sinclair, *Plant Dis. Rep.* **56**, 1054 (1972) [*CA* **78**, 80,711f (1973)]; C. S. Helling, D. G. Dennison, and D. D. Kaufman, *Phytopathology* **64**, 1091 (1974) [*CA* **83**, 73,221w (1975)].

<sup>495</sup> H. Siltanen and C. Rosenberg, *Publ. State Inst. Agric. Chem. (Finl.)* (1976), [*CA* **88**, 73,154e (1978)].

<sup>496</sup> Anonymous, *Fed. Regist.* **43**, 22,973 (1978) [*CA* **89**, 106,018q (1978)].

<sup>497</sup> Anonymous, *Kongetsu no Noyaku* **23**, 364-366 (1979) [*CA* **92**, 175,576u (1980)].

<sup>498</sup> S. Hayashi, K. Nishio, T. Nishimura, and K. Takita (to Kumiai Chemical Industry Co.), Japanese Patent 12,037 (1974) [*CA* **81**, 22,276u (1974)].

<sup>499</sup> S. Kawada, K. Nishio, and K. Takita (to Kumiai Chemical Industry Co.), Japanese Patent 4241 (1975) [*CA* **83**, 2276g (1975)].

<sup>500</sup> K. Nishio, I. Chiyomaru, E. Ishihara, S. Sasaki, and K. Konya, Japanese Patent 89,535 (1975) [*CA* **83**, 173,914t (1975)].

<sup>501</sup> J. Bader, H. Hamboek, E. Sturm, and A. G. Weiss (to Ciba-Geigy A.G.), Swiss Patent 574,708 (1976) [*CA* **85**, 88,510e (1976)].

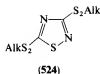
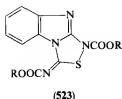
<sup>502</sup> J. H. Reisdorff, W. Brandes, H. Scheinpflug, B. Homeyer, and P. Roessler (to Bayer A.G.), German Patent 2,533,604 (1977) [*CA* **87**, 147,051x (1977)].

<sup>503</sup> J. Krenzer and S. B. Richter (to Velsicol Chemical Co.), U.S. Patent 3,764,685 (1973) [*CA* **80**, 92,001d (1974)].

<sup>504</sup> C. H. Cronin (to Fisons Ltd.), U.S. Patent 4,141,716 (1979) [*CA* **90**, 163,341j (1979)].

<sup>505</sup> Y. Yasuda, Y. Soeda, A. Ueda, S. Kano, and Y. Kato (to Nippon Soda Co.), Japanese Patent 8,852 (1974) [*CA* **81**, 164,732p (1974)].

<sup>506</sup> K. Nakamigawa, R. Takaoka, and T. Nakahama (to Nitto Chemical Industry Co.), Japanese Patent 00247 (1971) [*CA* **75**, 117,601m (1971)].



## VI. Technical Applications

In addition to their important well-established applications as pesticides, herbicides, and azo dyes, described separately in the appropriate Sections (see IV,C; IV,E,4; V), 1,2,4-thiadiazoles are of actual or potential value in several technical fields. Derivatives incorporating sulfur-containing functions are especially prominent in this context.

In rubber technology, the use of mercapto-1,2,4-thiadiazoles for several purposes<sup>507-510</sup> has been described. Both monomeric<sup>511</sup> and polysulfide structures<sup>512</sup> are suitable rubber cross-linking agents. Polyethylene sheet is stabilized and protected by the addition (0.5%) of 2,4-dimethyl-1,2,4-thiadiazolidine-3,5-dithione.<sup>513</sup> Poly(thiadiazolyl tetrasulfide) similarly stabilizes poly(vinylpyridines).<sup>514</sup>

Bis(dithio)thiadiazoles (e.g., **524**)<sup>113,515</sup> and bis(thiosulfenamides)<sup>516</sup> are employed as corrosion inhibitors in lubricants. The antiwear and extreme-pressure properties of lubricating greases are improved by the addition of (polymeric) 3,5-dimercapto-1,2,4-thiadiazole,<sup>517</sup> 2,4-dialkyl-1,2,4-thiadiazole-

<sup>507</sup> C. D. Trivette (to Monsanto Co.), U.S. Patent 3,869,435 (1975) [CA 83, 44,520n (1975)].

<sup>508</sup> M. W. Harman (to Monsanto Co.), U.S. Patent 3,899,502 (1975) [CA 83, 194,869x (1975)].

<sup>509</sup> J. J. D'Amico (to Monsanto Co.), U.S. Patent 3,904,619 (1975) [CA 84, 6300d (1976)].

<sup>510</sup> V. A. Ignatov, G. A. Blokh, N. V. Zorkin, Y. S. Rudoi, R. A. Akchurina, and L. M. Agafonova, *Tezisy Dokl.—Simp. Khim. Tekhnol. Geterotsikl. Soedin. Goryuch. Iskop.*, 2nd, 1973, 113 (1973) [CA 85, 144,378g (1976)].

<sup>511</sup> C. D. Trivette (to Monsanto Co.), German Patent 2,256,511 (1973) [CA 79, 54,674x (1973)].

<sup>512</sup> C. D. Trivette (to Monsanto Co.), U.S. Patent 3,979,369 (1976) [CA 86, 18,094u (1977)].

<sup>513</sup> A. F. Kopacki (to Stauffer Chemical Co.), U.S. Patent 3,338,865 (1967) [CA 67, 82,719m (1967)].

<sup>514</sup> J. T. Dunn and D. T. Manning (to Union Carbide Corp.), U.S. Patent 3,158,615 (1964) [CA 62, 11,973 (1965)].

<sup>515</sup> D. E. Ripple (to Lubrizol Corp.), U.S. Patent 3,904,537 (1975) [CA 84, 7432k (1976)].

<sup>516</sup> S. J. Brois and T. Colclough (to Exxon Research & Engineering Co.), German Patent 2,635,568 (1977) [CA 86, 189,960c (1977)].

<sup>517</sup> J. P. King, E. A. Mailey, and C. Popoff (to Pennwalt Corp.), U.S. Patent 4,107,059 (1978) [CA 90, 154,577p (1979)].

lidine-3,5-diones,<sup>518</sup> or 5-chloro-3-ethylthio-1,2,4-thiadiazole.<sup>133</sup> Flame-retarding properties have been claimed for 5-imino-4-methyl-1,2,4-thiadiazoline<sup>519</sup> and for 3,5-bis(tribromomethyl)-1,2,4-thiadiazole,<sup>520</sup> and their use as fireproofing agents in polymers has been discussed.<sup>520</sup>

In photography, mercapto- and alkylthio-1,2,4-thiadiazoles are useful in aiding several operations. They share these properties with other heterocyclic structures incorporating thiol-thione systems, and often form part of sweeping patent claims covering large numbers of compounds. Their applications are based on their photosensitizing properties,<sup>521,522</sup> their stabilizing action on photographic films,<sup>523,524</sup> their retarding effect on photographic development,<sup>525</sup> and their ability to improve blue-black tones.<sup>526</sup> 1,2,4-Thiadiazoles are structural constituents of dyes that act as sensitizers or as stabilizers in dry photographic processes.<sup>527-532</sup>

### ANALYTICAL

1,2,4-Thiadiazolylsulfenamides may be estimated volumetrically by a method based on their oxidation with bromine, the end point being indicated

<sup>518</sup> D. F. Gavin, F. J. Milnes, and J. R. Parziale (to Olin Corp.), U.S. Patent 4,183,816 (1980) [CA 92, 183,481z (1980)].

<sup>519</sup> K. Ishizuka (to Daiichi Lacc Manufacturing Co.), Japanese Patent 5,439 (1974) [CA 82, 59,824t (1975)].

<sup>520</sup> H. Hagen, H. Naarman, and K. Penzien (to BASF A.G.), German Patent 2,734,926 (1979) [CA 90, 205,217f (1979)].

<sup>521</sup> E. Inoue, H. Kokado, and T. Yamase, German Patent 2,215,474 (1973) [CA 80, 54,530t (1974)].

<sup>522</sup> H. Oehlschlaeger and O. Riester (to Agfa-Gevaert A.G.), German Patent 2,348,737 (1975) [CA 84, 52,078k (1976)].

<sup>523</sup> G. L. Hiller (to Eastman Kodak Co.), German Patent 2,127,169 (1971) [CA 76, 119,948z (1972)].

<sup>524</sup> R. M. Cole (to Eastman Kodak Co.), German Patent 1,923,824 (1969) [CA 72, 105,870y (1970)].

<sup>525</sup> V. I. Sheberstov and B. A. Shashlov, *Zh. Nauchn. Prikl. Fotogr. Kinematogr.* 6, 413 (1961) [CA 58, 6369 (1963)].

<sup>526</sup> C. Holstead (to Kodak Ltd.), British Patent 972,063 (1964) [CA 62, 165 (1965)].

<sup>527</sup> H. Kampfer, H. Oehlschlaeger, and W. Gesierich (to Agfa-Gevaert A.G.), U.S. Patent 3,635,706 (1972) [CA 77, 21,592z (1972)].

<sup>528</sup> H. Kampfer, J. Goetze, A. von Koenig, and H. Oehlschlaeger (to Agfa-Gevaert A.G.), German Patent 2,042,531 (1972) [CA 77, 68,574k (1972)].

<sup>529</sup> H. Oehlschlaeger, O. Riester, T. H. Ghys, K. E. Verhille, and J. Vanheertum (to Agfa-Gevaert A.G.), German Patent 2,121,014 (1972) [CA 78, 104,468k (1973)].

<sup>530</sup> N. Baumann (to Ciba-Geigy A.G.), German Patent 2,525,673 (1976) [CA 85, 12,371q (1976)].

<sup>531</sup> T. Eida and I. Endo, German Patent 2,558,951 (1976) [CA 86, 148,796k (1977)].

<sup>532</sup> H. Kobayashi, Y. Yano, and I. Endo, German Patent 2,702,919 (1977) [CA 89, 34,144c (1978)].

amperometrically.<sup>533</sup> The microanalytical determination of carbon in 3- and 5-substituted 1,2,4-thiadiazoles is improved by the use of an additional silver gauze in the universal packing of the microcombustion tube.<sup>534</sup> The chromatographic separation and identification of some 100 pesticides included 1,2,4-thiadiazole derivatives.<sup>535</sup> 5-Chloro-3-phenyl-1,2,4-thiadiazole has been identified in waste effluents from dye-manufacturing plants.<sup>536</sup>

<sup>533</sup> A. P. Kreshkov, M. I. Lebedeva, and R. V. Borisova, *Tr. Mosk. Khim.-Technol. Inst.* **75**, 161 (1973) [*CA* **82**, 59,438v (1975)].

<sup>534</sup> J. Saran, P. N. Khanna, and S. Banerji, *Indian J. Chem.* **1**, 362 (1963).

<sup>535</sup> H. Nagayoshi, K. Suzuki, and T. Kashiwa, *Noyaku Kensasho Hokoku* **15**, 22 (1975) [*CA* **85**, 73,260z (1976); **86**, 38,455r (1977)].

<sup>536</sup> L. M. Games and R. A. Hites, *Anal. Chem.* **49**, 1433 (1977).

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